

Novel Chiral Hypervalent Iodoarenes In
Enantioselective Iodocatalysis and Oxidation
Reactions

Sabine Altermann

Ph.D. Thesis Winter 2008

Cardiff University

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Novel Chiral Hypervalent Iodoarenes In Enantioselective Iodocatalysis and Oxidation Reactions

A thesis submitted for the degree of a
Doctor of Philosophy
at Cardiff University

by

Sabine Altermann

December 2008

Declaration

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Signed S. Altermann (S. Altermann)

Date 23.01.09

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For my Parents

Alexa and Heinz Altermann

for great support and love throughout all my life

For my Partner

Thomas Diehl

for amazing love and friendship when needed most

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- EPSRC Swansea Mass Spec Service

Abstract

A range of enantiomerically pure iodine compounds has been synthesised and either oxidised to the corresponding hypervalent iodine compound and used as oxidant or employed as catalysts in a range of reactions together with different oxidants in stoichiometric amounts in order to form the respective hypervalent iodine species *in situ*. Three different enantioselective catalytic reactions have been investigated: α -acetoxylation of ketones, halolactonisation of pentenoic acids and α -oxytosylation of ketones. Also – probably for the first time – alkyl iodides have been employed as catalysts in these transformations.

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Abbreviations

List of Abbreviations

Ac	acetyl
BINOL	1,1'-Bi(2-naphthol)
Bu	butyl
CDCl ₃	deuterated chloroform
d	doublet
δ	chemical shift (ppm)
DIB	(diacetoxyiodo)benzene
DHP	dihydropyran
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMSO	deuterated dimethylsulfoxide
ee	enantiomeric excess
eq	equivalent
ESI	electrospray ionisation (mass spectrometry)
Et ₃ N	triethylamine
FIBX	Tetrafluoro- <i>o</i> -iodoxybenzoic acid
FREON	1,1,2-trichlorotrifluoroethane
h	hours
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IBA	2-iodosobenzoic acid
IBX	2-iodoxybenzoic acid
IR	infrared
<i>J</i>	coupling constant
LDA	lithium diisopropylamide
LICA	lithium cyclohexylisopropylamide
LRMS	low resolution mass spectrometry
m	multiplet
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid

Abbreviations

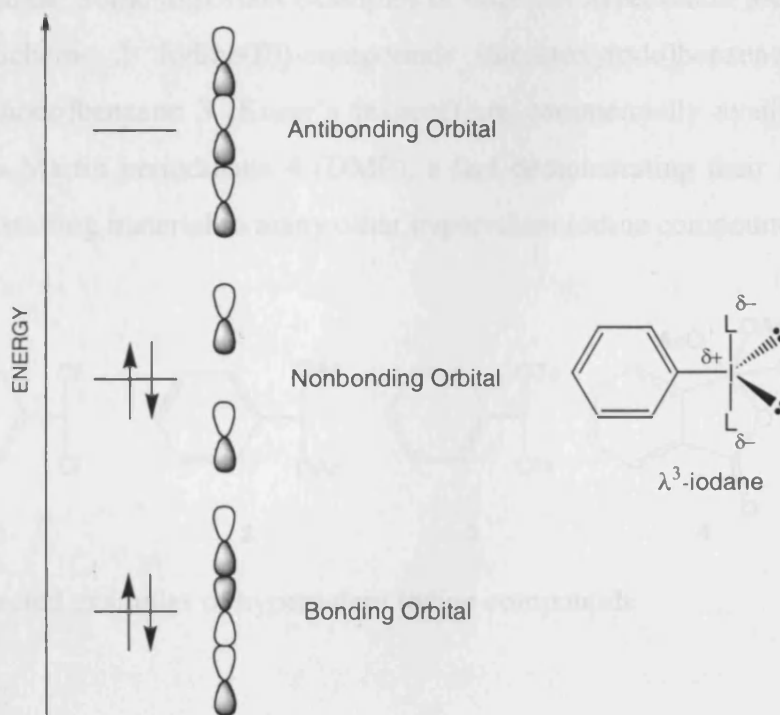
m/z	mass to charge ratio
Me	methyl
min	minute
mol	mole
m.p.	melting point
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance (spectroscopy)
ppm	parts per million
Ph	phenyl
PPNO	4-phenylpyridine <i>N</i> -oxide
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
q	quartet
R	general (alkyl) group
r.t.	room temperature
t	triplet
TADDOL	(4 <i>R</i> ,5 <i>R</i>)-2,2-Dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyldioxolane-4,5-dimethanol
TBS	<i>tert</i> -butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N, N, N', N'</i> -tetramethylethylenediamine
TMS	tetramethylsilyl
TsOH	<i>p</i> -toluenesulfonic acid

1 Hypervalent Iodine Compounds

1.1 Introduction

1.1.1 Bonding Structure and Examples.

The first to synthesise a polycordinated iodine compound – (dichloriodo)benzene **1** was C. Willgerodt in 1886.^[1] After his discovery, this new class of compounds did not prove to be synthetically useful for several decades; only in the last three decades and after development of several powerful iodanes interest in this class of compounds has increased highly.^[2,3] Also, the term “hypervalent”^[4] iodine compound can be used; it describes the kind of bonding system of these compounds. Generally, polycordinated iodine compounds are composed of one covalent bond, usually to an arene, and one or two hypervalent bonds, leading to two kinds of hypervalent compounds, possessing either monovalent ligands L (RIL₂ or RIL₄) or bivalent ligands Z (not bidentate ligands; RIZ, RIZ₂ or RIZL₂). In these compounds, the bond of the iodine to a bivalent ligand formally is a double bond (two centre-four electron bond), but it is considered rather as a polar RI⁺–Z[–] bond.^[5] Bivalent ligand Z can be an oxygen or an organic electronegative group connected to iodine *via* a carbon or nitrogen atom.



Scheme 1 Hypervalent bonding system in λ^3 -compounds.

The iodine atom forms three-centre-four-electron bonds (3c-4e bond) to monovalent ligands, usually an electronegative atom or group.^[5] The two ligands are located in the axial positions of a trigonal bi-pyramid, while the less electronegative arene moiety is placed in the equatorial position, thus forming a T-shaped compound. The often aromatic substituent forms a covalent bond to the singly occupied 5p orbital of the iodine atom lying in the equatorial position of a trigonal bipyramid, whereas the two electronegative ligands are attached to one of the doubly occupied 5p orbitals of the iodine atom, one to each lobe and in axial positions (Scheme 1).

The bond lengths of the covalent bond in compounds **1–3** is approximately the sum of the radii of the carbon and the iodine atom (2.102 Å), whereas for the heteroatom ligands the radii are longer than the respective sum, e.g. the I–O bond length in **2** is 2.15–2.16 Å but the sum of the covalent radii is only 1.99 Å.^[6]

Another hypervalent bond to two more electronegative ligands would be located orthogonal to the first hypervalent bond, forming a square-planar arrangement (Figure 1).^[7] In these hypervalent bonds, one orbital of the iodine atom participates to two 3c-4e bonds, which are longer and weaker than the covalent bond, thus forming potential leaving groups during reactions.^[8] At present, most important classes are iodine (III) derivatives (λ^3 -iodanes) furnished with two electronegative ligands and iodine (V) compounds (λ^5 -iodanes) furnished with four electronegative ligands. Some important examples of different hypervalent iodine compounds are outlined in Scheme 2. Iodine(III)-compounds (diacetoxyiodo)benzene **2** (DIB) and [hydroxy(tosyloxy)iodo]benzene **3** (Koser's reagent) are commercially available as well as the iodine(V)-Dess-Martin periodinane **4** (DMP), a fact demonstrating their synthetic value. Iodane **2** serves as starting material to many other hypervalent iodine compounds.

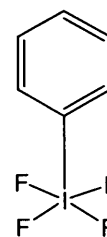
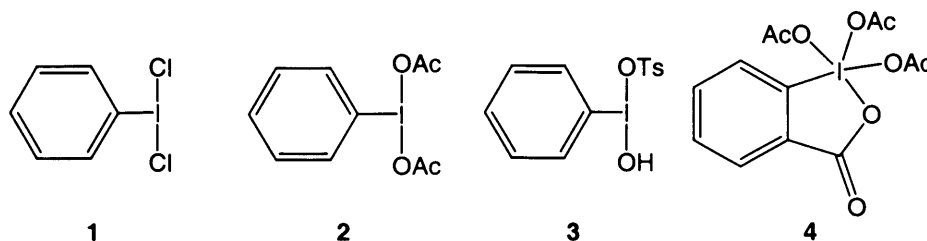


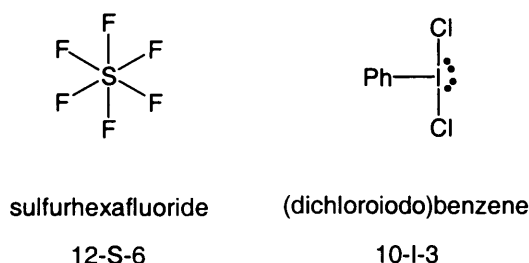
Figure 1



Scheme 2 Selected examples of hypervalent iodine compounds

1.1.2 Nomenclature

A nomenclature system for molecules with hypervalent bonding has been established by Perkins and co-workers in 1980.^[9] Not only iodine compounds but also other hypervalent molecules such as sulphur compounds were classified in this manner (Scheme 3). The bonding system of an atom X containing N electrons in the valence shell connected to L ligands is described as an N -X- L system; alternatively, these compounds can be described as λ^L -compounds, thus assigning the number of ligands attached. According to this system, compounds **1–3** can be referred to as λ^3 - or 10-I-3 and compound **4** as λ^5 - or 10-I-5 compound.



Scheme 3 Nomenclature of hypervalent compounds.

1.1.3 Reactions

The interest in hypervalent iodine has grown among other reasons because of their properties being very similar to those of Hg(II), Tl(III) and Pb(IV), which have traditionally been used for oxidations and selective functionalisations in the past. Therefore, the environmentally benign iodine compounds can replace toxic heavy-metals.^[6] They can be employed as oxidation reagents as well as electrophilic reagents e.g. for functionalisation reactions of alkenes and subsequent iodolactonisations,^[10] dioxytosylations^[11] or α -oxytosylations.^[12] For oxidation reactions mainly 2-iodoxybenzoic acid (IBX) or respective derivatives are used; among the oxidation reagents, DMP **4** is one of the most potent reagents. It conveniently oxidises primary and secondary alcohols at room temperature to aldehydes and ketones, respectively.^[5] For functionalisation reactions, mostly λ^3 -compounds as well as their polymer-supported derivatives are used.^[13-19] Generally, in their reactions with nucleophiles, after substitution at the iodine atom usually reductive elimination of iodobenzene is observed together with ligand transfer to a substrate, which is then oxidised.^[20]

However, investigations especially in the synthesis of and reactions with enantiomerically pure hypervalent iodine compounds have to be accomplished in order to enlarge the possibilities of employment of these compounds.

In the following, an introduction to each chapter is given separately, related to the topics discussed in the respective chapter.

1.2 Literature

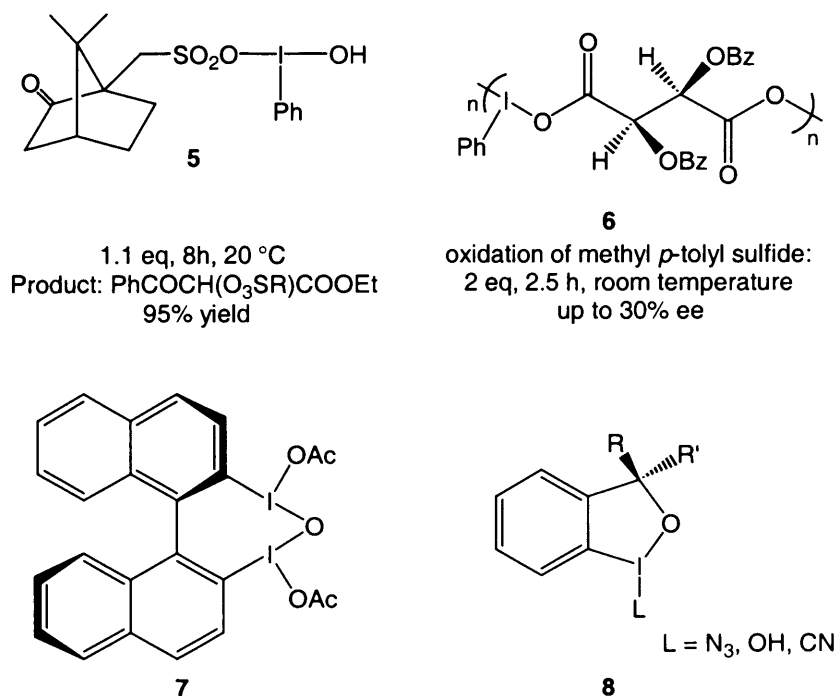
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2 Synthesis of Chiral Iodine Compounds

2.1 Introduction

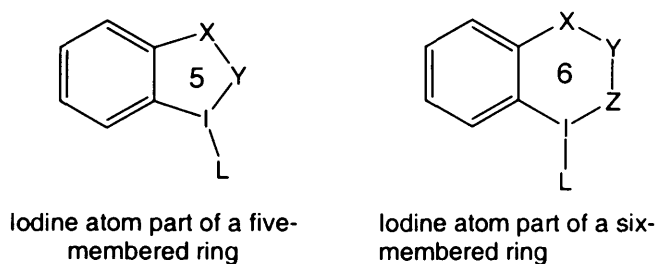
2.1.1 First Chiral Hypervalent Iodine Compounds

Recently, chiral hypervalent iodine(III) compounds have been synthesised and employed. They are either derived from camphorsulfonic acid (**5**),^[1] tartaric acid (**6**),^[2] binaphthalene (**7**)^[3] or benziiodoxole (**8**)^[4,5] and have been used for the α -functionalisation of carbonyl compounds or the oxidation of sulfides to sulfoxides (Scheme 1). Polymeric tartrate **6** was employed in the oxidation of methyl *p*-tolyl sulfide together with either DIB **2** or iodosylbenzene and the corresponding sulfoxide was obtained with 21% *ee* and 30% *ee*, respectively. The binaphthalene derivative **7** is the decomposition adduct of the corresponding bi(diacetoxyiodo)binaphthalene when left in solution at room temperature. Cyanobenziiodoxole **8** can be employed for e.g. as cyano transfer reagent toward *N,N*-dialkylarylamines.^[6]



Scheme 1 First chiral hypervalent iodine compounds.

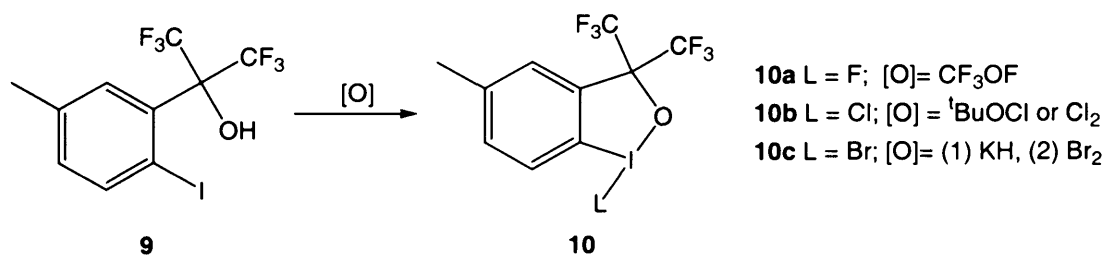
In the following, the term “precursors to five- or six-membered ring iodanes” will be used, indicating the ring size of the heterocycles of the corresponding oxidised compounds incorporating the side chain on the aromatic ring in the *ortho*-position to the iodine atom and the iodine atom itself. X, Y and Z are unspecified atoms as well as L, which indicates only generally, that these compounds are oxidised λ^3 -iodoarenes.



Scheme 2 Annotation for the nomenclature used in the following.

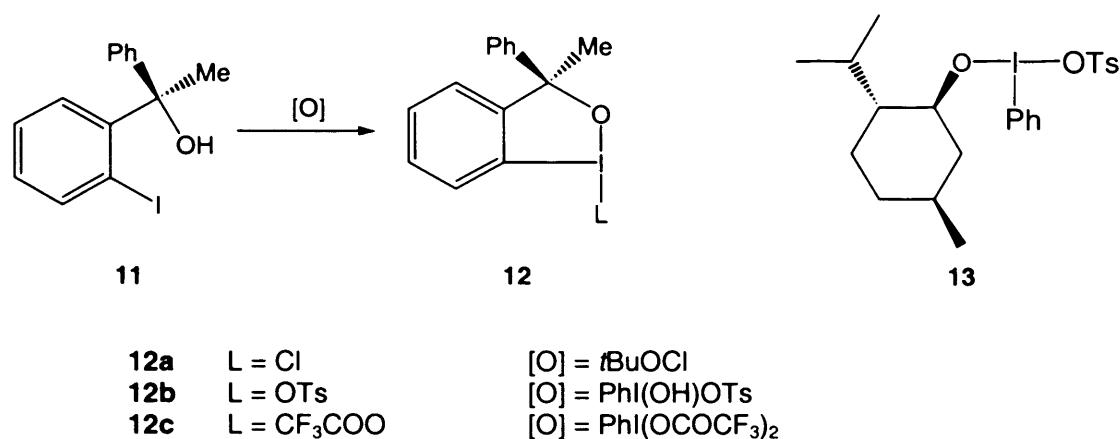
2.1.2 Precursors to Five-Membered Ring Iodinanes

Cyclic iodanes containing a five-membered ring were first described in 1909 by Thiele and Peter.^[7] The advantage of five-membered iodine heterocycles, benziodoxoles, over non-cyclic reagents is the increased stability allowing the preparation of otherwise unstable derivatives with I-Br, I-OOR, I-N₃ and I-CN bonds.^[8] This phenomenon is explained by the bridging of the apical and equatorial positions by a five-membered ring. In 1979 Amey and Martin were able to isolate the stable cyclic iodanes **10** containing internal alkoxy ligands (Scheme 3).^[9] Besides the five-membered ring, additional stabilisation was gained by the highly electronegative trifluoromethyl substituents in **10**; these fluorinated compounds are experienced to be far more stable than their simple methyl analogues and could not be hydrolysed easily to the respective hydroxyiodinane upon treatment with aqueous potassium hydroxide.^[9]



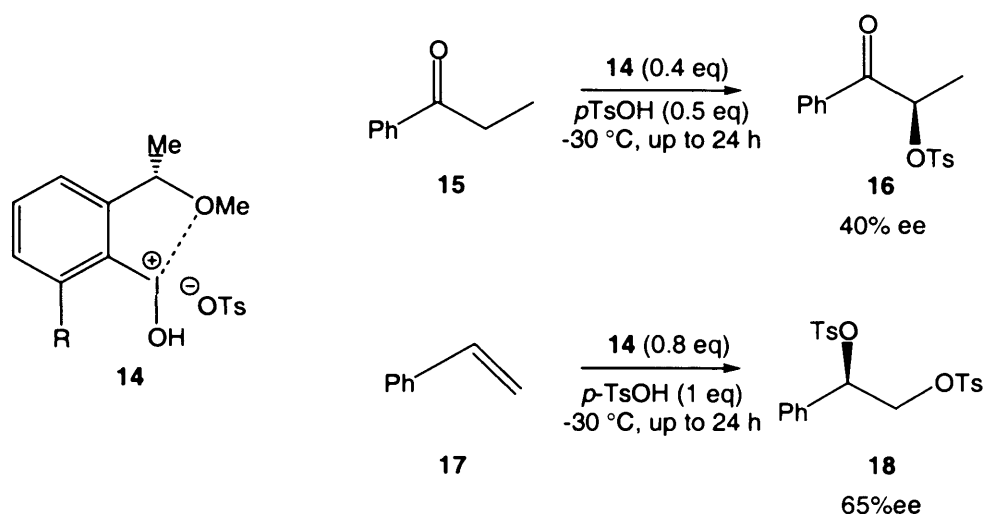
Scheme 3 Synthesis of stable I-haloiodinanes **10a–c**.

Later, Zhdankin and co-workers synthesised the respective 1-azido^[10] and 1-cyano^[6] analogues. Tricyclic bis(alkoxy)iodanes were prepared by Nguyen and co-workers.^[11,12] Asymmetric benziiodoxoles **12** were prepared by oxidation of **11** (Scheme 4) by Koser and Rabah.^[4] Most of the chiral hypervalent iodine compounds known so far bear a chiral substituent on the iodine (e.g. compounds **5**, **6** and **13**),^[13] whereas the chiral moieties in compounds of type **12** are fixed in *ortho*-position to the iodine.



Scheme 4 Five-membered ring stabilised iodinanones **12**.

Wirth and co-workers developed chiral hypervalent iodine compounds of type **14**. Iodane **14** is furnished with a substituent in the arene moiety and a chiral moiety in the *ortho*-position to the iodine atom. Compound **14** was employed for oxytosylation reactions of propiophenone **15** and styrene **17** and resulted in promising enantioselectivities and conversions (Scheme 5). The α -oxytosylation reaction was conducted using 0.5 eq of *p*TsOH•H₂O and 0.4 eq of **14** in CH₂Cl₂ at –30 °C for up to 24 hours, whereas the reaction using styrene as starting material required 1 eq of *p*TsOH•H₂O and 0.8 eq of **14**. In this manner, synthetically valuable^[14,15] tosylates such as **16** and **18** were obtained in up to 40% *ee* (Reaction A) and 65% *ee* (Reaction B), when the *ortho*-substituent on the aromatic ring was an ethyl group.

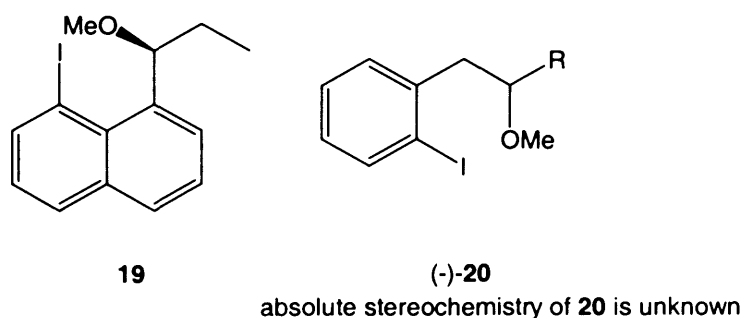


Scheme 5 Enantioselective oxytosylation reactions of propiophenone **15** and styrene **17**.

A crystal structure of compound **14** without an *ortho*-substituent on the aromatic ring (*R* = H) was obtained.^[13] A strong interaction between the iodine atom and the methoxy-oxygen was found; the distance measured (2.47 Å) was less than the distance between iodine and the closest oxygen of the tosyl group (2.82–3.2 Å), as formula **14** indicates. Therefore, these compounds can also be regarded as salts of *p*-toluenesulfonic acid.

2.1.3 Precursors to Six-Membered Ring Iodanes

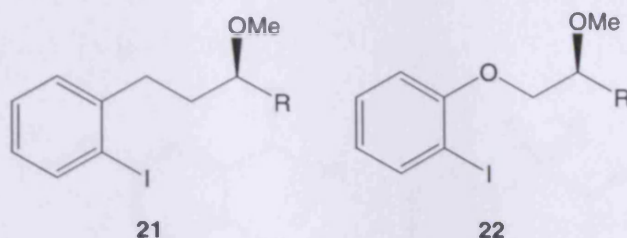
Investigations to the influence of a larger-size ring to stabilisation of these compounds are necessary. Wirth and co-workers synthesised enantiomerically pure iodoarenes **19** and **20**,^[16] but no successful oxidation of **19** and **20** to the respective hypervalent compounds is reported to this date (Scheme 6).



Scheme 6 Enantiomerically pure precursors to six-membered ring iodanes.

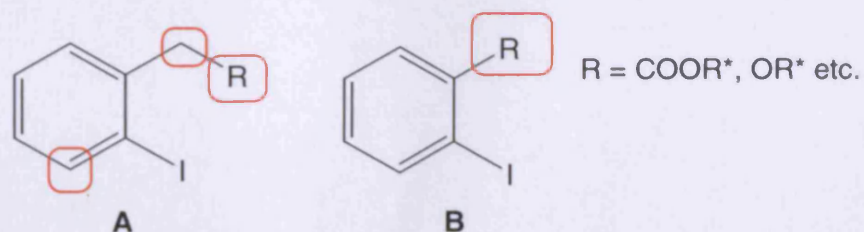
2.1.4 Precursors to Seven-Membered Ring Iodanes

Also, chiral iodoarenes **21** and **22** were developed by Wirth and co-workers in order to investigate the influence of shifting the chiral moiety further away from the iodine atom (Scheme 7).^[16] Ether **21** was oxidised to the respective bis(trifluoroacetoxyiodo)arene in moderate yields using H_2O_2 -urea and trifluoroacetic anhydride.^[17]

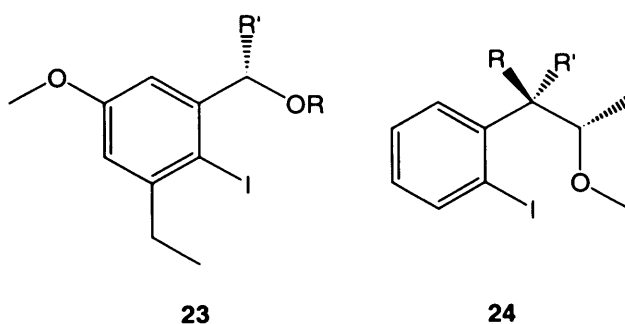


Scheme 7 Potential seven-membered ring benziodoxoles.

2.1.5 Project Outline. The synthesis of new enantiomerically pure iodoarenes is planned. Iodoarenes furnished with a side chain in *ortho*-position allows the introduction of one or several asymmetric centres as well as the insertion of heteroatom moieties are of great advantage. Skeletal structures of proposed iodoarenes are shown below. Structure **A** is furnished with a longer side chain in *ortho*-position to the iodine atom. The group R can contain different functional groups such as esters or ethers containing an asymmetric moiety. Also, introduction of substituents in the benzylic position would create a chiral centre even closer to the iodine atom. In addition, a substituent at the aromatic ring in *ortho*-position to the iodine atom has proven to be very valuable before.^[13] Similar functional groups can be introduced into structure **B**, only the side chain in *ortho*-position to the iodine atom is shorter. In this way, the optimum length of this side chain can be determined as well as the influence of different functional groups and asymmetric moieties.



Compounds **23** and **24** combine these features and the synthetic pathway towards these iodoarenes was the starting point of this project (Scheme 8). In addition, ether **23** can be furnished with an ethyl substituent on the aromatic ring in the *ortho*-position to the iodine atom. In order to investigate the influence of additional groups at the aromatic ring, the introduction of an electron-donating methoxy group in *para*-position was planned. Ether **24** allows the investigation of the influence of a prolonged side chain, where several additional stereogenic centres can be created.

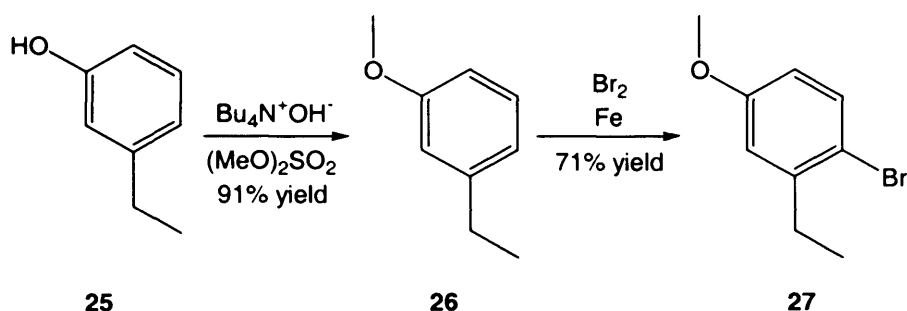


Scheme 8 Chiral target molecules **23** and **24**.

2.2 Results and Discussion

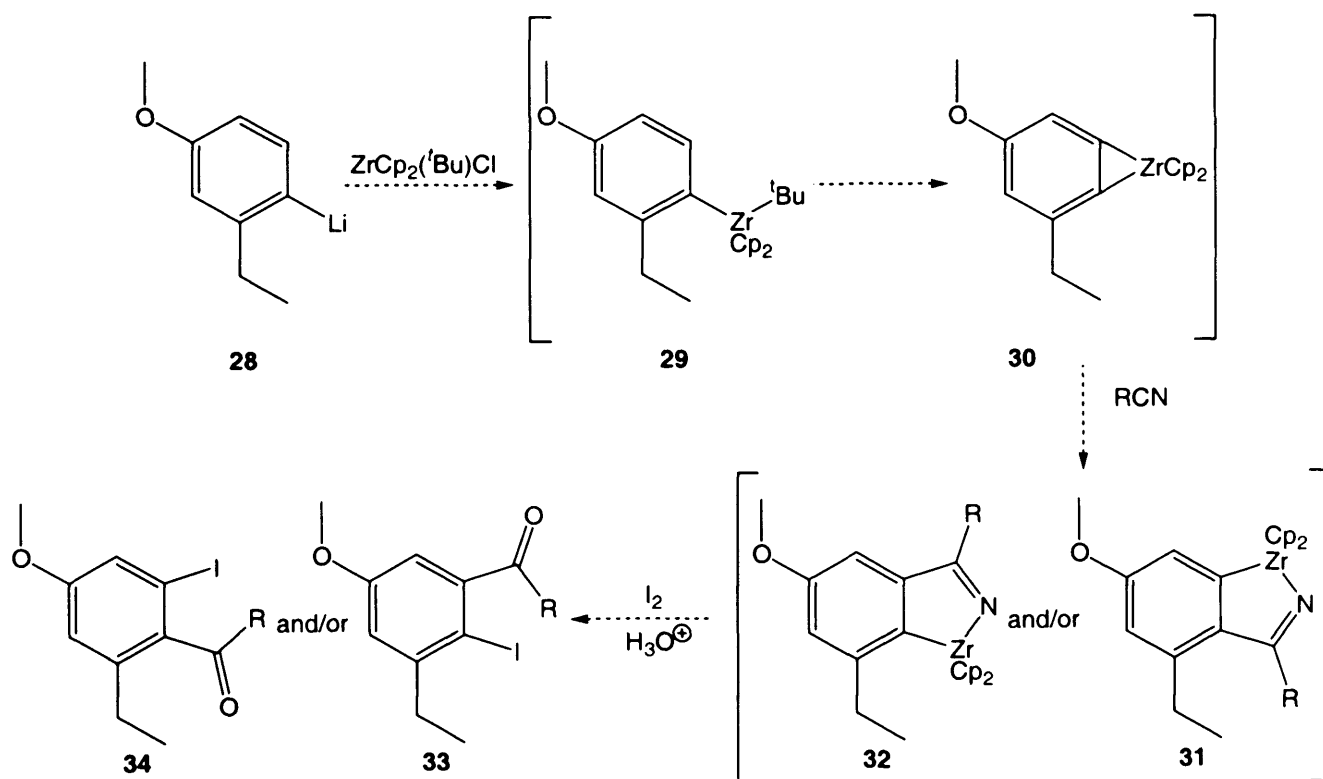
2.2.1 Precursors to Five-Membered Ring Iodanes

Arylbromide **27** has been synthesised before by Nelson and co-workers (Scheme 9).^[18] The first reaction step towards a derivative of **23** is the phase-transfer catalysed methylation of commercially available 3-ethylphenol **25** to give 3-methoxyethylbenzene **26** in nearly quantitative yields. Subsequent bromination in exclusively *para*-position to the methoxy group afforded bromoethylanisole **27** in good yields (71%).



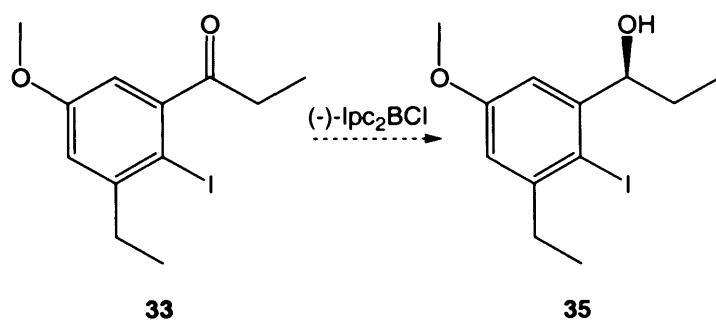
Scheme 9 Synthesis of 4-bromo-3-ethylanisole **27**.^[18]

The next reaction step planned towards iodoarene **35** was the formation of propiophenone **34** via a zirconocene stabilised intermediate **31/32**.^[19] The mechanism of the addition of the zirconocene complex is shown in Scheme 10.



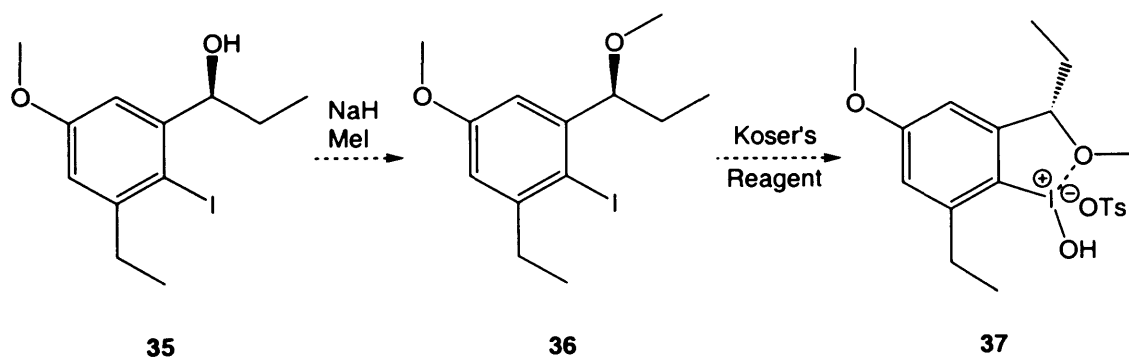
Scheme 10 Proposed mechanism of the addition of the zirconocene complex.

After the bromine/lithium exchange in compound **27** to **28**, the zirconocene complex substitutes the lithium atom followed by elimination of *t*-butane and formation of transition state **30**; leading to compound **31** and/or **32** after insertion of a suitable nitrile. Finally, hydrolysis and iodination give iodoarene **33** and/or **34**. Subsequent asymmetric reduction using (–)-*B*-diisopinocampheyl chloroborane was expected to give the respective alcohol **35** (Scheme 11).^[20]



Scheme 11 Asymmetric reduction of phenone **33**.

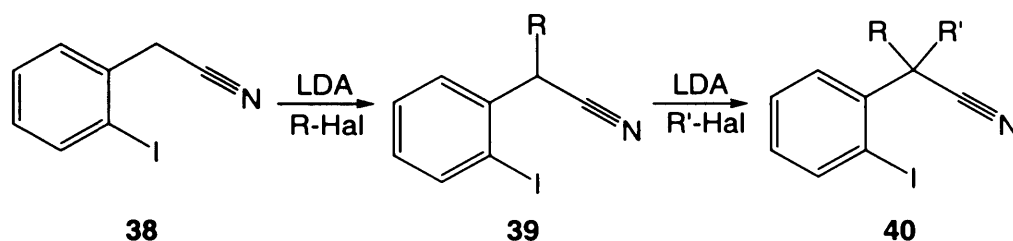
Methylation of alcohol **35** followed by oxidation using Koser's reagent was then expected to result in target molecule **37** (Scheme 12).^[21] However, the synthesis of phenone **33** remained unsuccessful and this synthetic pathway was abandoned from here.



Scheme 12 Final synthetic steps towards five-membered iodane **37**.

2.2.2 Precursors to Six-Membered Ring Iodanes

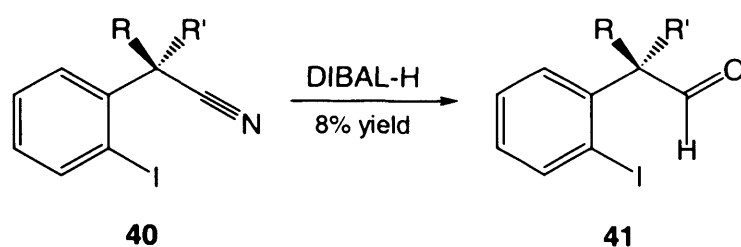
Nitriles **40** were synthesised in the past by Pascal and co-workers.^[22] Synthesis of **40** started from commercially available prochiral 2-iodoacetonitrile **38** (Table 1). Nitrile **38** was alkylated once or twice in iterative steps using LDA and an alkylhalide in 71–92% overall yields. The substitution reaction using ethyliodide (entry 2) gave good conversion of 75% but only moderate yield due to necessary excessive purifications with column chromatography and preparative TLC. However, this synthetic pathway allows a convenient variation of the substituents.



Entry	Compound	R	R'	overall Yield (%)
1	39a	Me	H	97
2	39b	Et	H	41
3	40a	Me	Me	71
4	40b	Et	Et	92
5	40c	Me	Bn	88

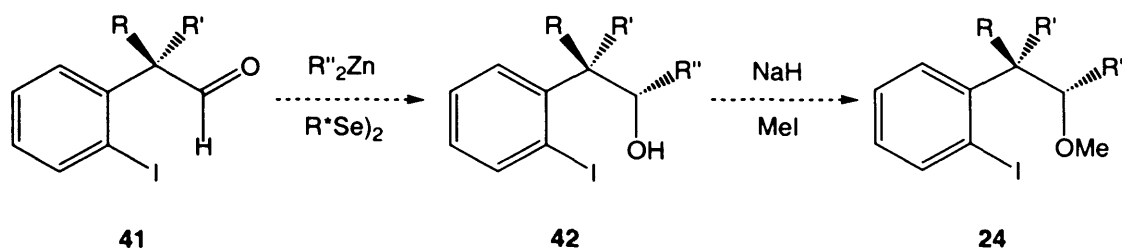
Table 1 Alkylations of prochiral nitrile **38**.

The enantiomers of nitriles **39** and **40** were resolved by preparative HPLC on a chiral stationary phase in order to employ enantiomerically pure compounds **39** and **40** in enantioselective reactions. The following step was the reduction of the nitriles to the corresponding aldehydes **41** using DIBAL-H (Scheme 13). In order to verify the literature procedure exactly, nitriles **40a** and **40b** furnished with two ethyl or two methyl groups respectively have been synthesised and used in reduction test reactions. In contrast to literature gaining up to 50%, yields achieved were only up to 8%.



Scheme 13 Reduction of substituted (2-iodophenyl)acetonitrile **40**.

Based on aldehyde **41**, stereoselective methylation using dialkyl zinc (R''_2Zn) together with a chiral diselenide catalyst^[23] to alcohol **42** – a well-established procedure in the Wirth group – was planned, with subsequent methylation of the alcohol using sodium hydride and methyl iodide (Scheme 14). Oxidation of iodoarene **43** was meant to be done using Koser's reagent in order to gain the respective λ^3 -derivative.^[21]



Scheme 14 Synthetic approach to iodoarene **24** planned.

2.2.3 Manipulation of the Nitrile Moiety

The reduction of nitriles **40** with DIBAL-H only resulted in very poor yields (Table 2, entry 1). It was thought that the iodine atom in compounds **40** could possibly have a detrimental influence in this reaction; therefore, phenylacetonitrile was employed under similar conditions, but here as well, only traces of the desired aldehyde were detected.

In order to develop a different synthetic pathway towards a derivative of iodoarene **24**, several methods were investigated for the manipulation of the nitrile moiety. When freshly prepared Grignard reagents were employed expected to yield in the respective carbonyl compound, only starting material was recovered (entries 3, 4). Also, strong inorganic bases were used in order to synthesise the respective carboxylic acid. Sodium hydroxide in methanol at room temperature and potassium hydroxide in ethylene glycol (heated up to 105 °C) were used, but only starting materials were isolated from the reaction mixtures in both

cases (entries 5, 6). The employment of acids did not result in the desired products either. Stirring of **39** or **40** in hydrochloric acid (concentrated as well as diluted) and methanol at room temperature did not yield the respective carboxylic acid (entries 7, 8); this reaction was also conducted in the microwave using 100–300 W for five to ten minutes at 50–65 °C, but in all reactions, only starting material was recovered. The employment of sulfonic acid also did not result in the respective carboxylic acid; once more, only starting material was recovered (entry 9). Starting material was also recovered from the reaction mixture, when trimethylsilylchloride in methanol was employed at 50 °C.^[24]

The manipulation of nitriles attached to quaternary carbon atoms is reported. Nitriles were refluxed together with hydrochloric acid.^[25] Now looking back, the reactions conducted with similar reagents should have been refluxed or irradiated in the microwave at higher temperatures and over a prolonged time period; alternatively, the quality of DIBAL-H should have been tested. Also, other functionalisation reagents such as tin dichloride^[26] or iron complexes^[27] could have been used.

Entry	Reagent	S.M.	43-R''	Yield [%]
1	DIBAL-H	40a ,	CHO	8
2	DIBAL-H	40b	CHO	0 ^a
3	MeMgI	40a	COCH ₃	0 ^a
4	MeMgI	40b	COCH ₃	0 ^a
5	NaOH, MeOH	40b	COOH	0 ^a
6	KOH	40a	COOH	0 ^a
7	HCl, MeOH	39	COOCH ₃	0 ^a
8	HCl, MeOH	40a	COOCH ₃	0 ^a
9	H ₂ SO ₄	39	COOH	0 ^a
10	TMSCl, MeOH	40a	COOCH ₃	0 ^a

a starting material was recovered.

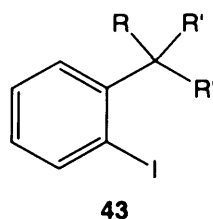


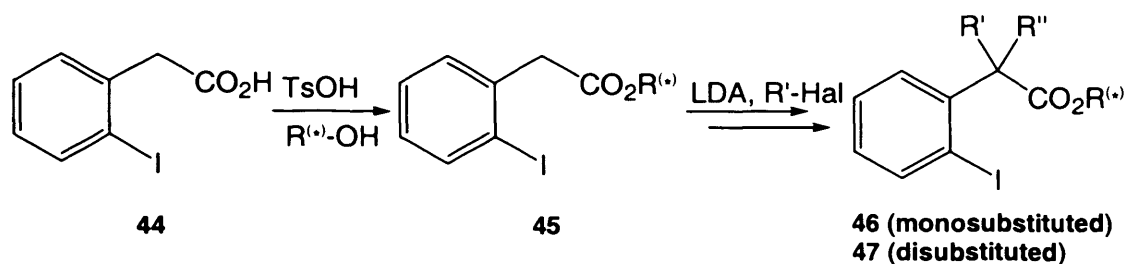
Table 2 Different attempted manipulation reactions of iodoaryl nitriles **39** and **40**.

This pathway was abandoned from here and enantiomerically pure nitriles **39** and **40** were used as reagents in different reactions (see following chapters).

2.2.4 Synthesis of Precursors of Chiral Six-Membered Ring Iodane Esters

A different approach towards iodoarenes **24** was planned *via* respective iodoarene esters, starting from commercially available 2-iodophenylacetic acid **44** (Table 3). The nature of the alcohol selected already allows introduction of differently bulky non-chiral as well as chiral groups in esters. Methanol was used as the smallest non-chiral reagent, whereas benzyl alcohol served as more hindered agent and finally terpene derived alcohols as chiral reagents. Terpenes and their derivatives have proven to be very powerful and versatile chiral auxiliaries and are very often used in natural product synthesis. Some examples of commonly used terpenes are given by e.g. pinene,^[28] camphor^[29] or limonene.^[30] After column chromatography, esters **45** were alkylated once or twice using LDA as base together with alkylhalides. If esters **45** were alkylated twice, no purification of the monosubstituted ester **46** was necessary, the crude reaction mixtures were alkylated once more after work-up and concentration straightaway.

The esterification of acid **44** using an alcohol together with *p*-toluenesulfonic acid as catalyst gave excellent conversions. Prochiral methyl ester **45a** is the least sterically hindered ester synthesised in good yields of 91%, followed by more hindered benzyl ester **45b** (87% yield); the respective reaction mixtures were stirred overnight in dichloromethane and purified by column chromatography. Esters **45c–e** furnished with a terpene moiety such as a borneyl-, menthyl-, or fenchyl-group were stirred at 60 °C in acetonitrile overnight and gave 60% (**45e**) to 99% (**45c**) yield. They can be used after purification for further reactions straightaway, thus providing an easy and high yielding approach towards chiral iodoarenes.

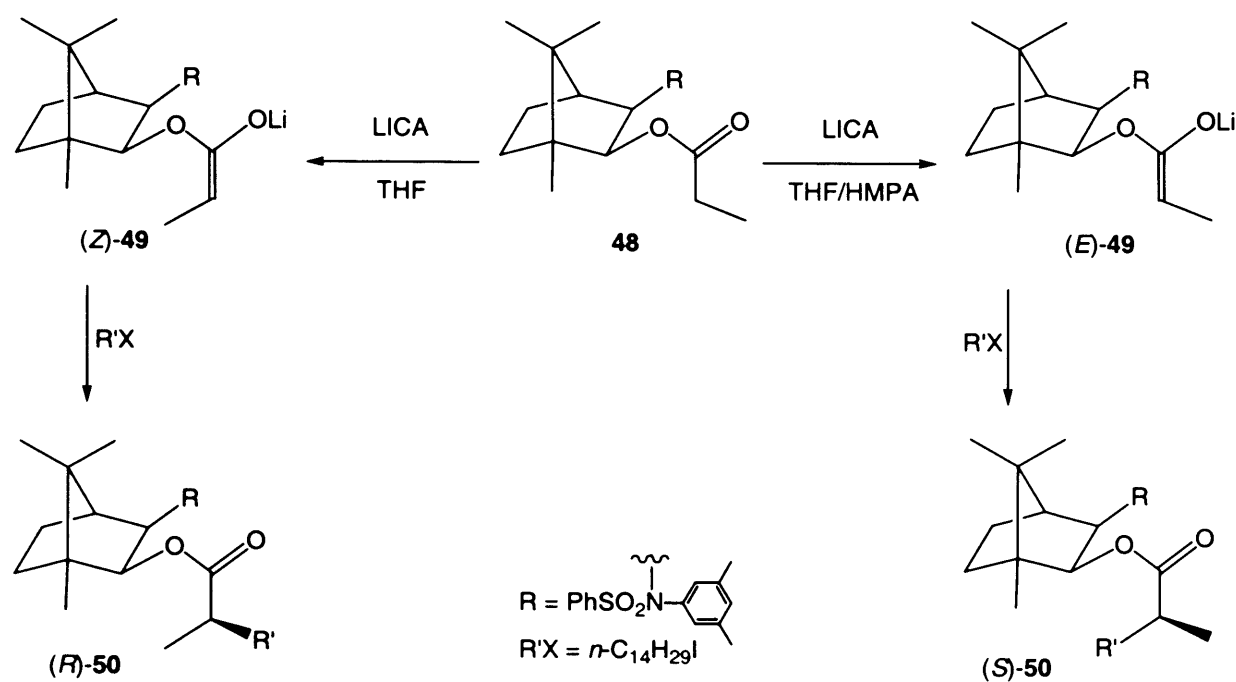


Nr	R ^(*)	R [']	R ^{''}	Yield % [overall]
45a	Methyl	H	H	91
45b	Benzyl	H	H	87
45c	(1 <i>S</i>)-Bornyl	H	H	99
45d	<i>L</i> -Menthyl	H	H	95
45e	(1 <i>R</i>)-Fenchyl	H	H	60
45f	Helmchen ^a	H	H	60
46a	Methyl	Methyl	H	71
46b	Methyl	Ethyl	H	95
46c	Methyl	Benzyl	H	85
46d	Benzyl	Methyl	H	95
46e	(1 <i>S</i>)-Bornyl	Methyl	H	41
46f	<i>L</i> -Menthyl	Methyl	H	90
46g	(1 <i>R</i>)-Fenchyl	Methyl	H	89
47a	Methyl	Methyl	Methyl	73 [52]
47b	Methyl	Methyl	<i>n</i> Pr	75 [53]
47c	Methyl	Methyl	Benzyl	75 [53]

^a this term was chosen as abbreviation for the ester moiety derived from compound **45f** (see below).

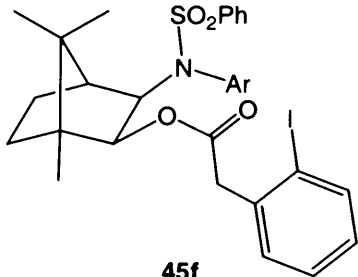
Table 3 Overview of different esters **45–47** synthesised.

The synthesis of ester **45f** originates from earlier work by Helmchen and co-workers.^[31] (+)-Camphor derived propionates **48** and their stereoselective alkylation using lithium cyclohexylisopropylamide (LICA) or a LICA/HMPA complex as bases (Scheme 15) were developed. In this reaction, not only conformational and steric effects caused by groups capable of shielding as well as complexation take influence, but also complexing interactions of the lithium atom with HMPA are considered to take place.

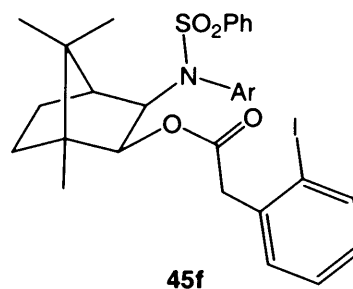


Scheme 15 Stereoselective alkylation of camphor derived propionates **48**.

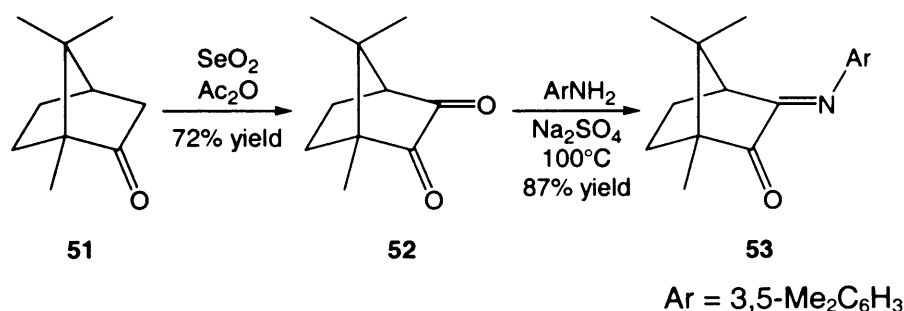
The formation of the isomeric enolates (*Z*)-**49** and (*E*)-**49** is kinetically controlled by LICA (lithium cyclohexylisopropylamide) and the LICA/HMPA complex. This fact was proven by trapping enolates **49** using TBS-Cl according to a method developed by Ireland and co-workers,^[32] yielding the respective silylketene acetals of **49** followed by their configurational determination ((*E*)-**49**:(*Z*)-**49** = 98:2 [LICA] and 4:96 [LICA/ HMPA]). Since this method seemed to be a promising method for stereoselective alkylation of the respective iodoarenes, synthesis of iodoaryl ester **45f** was accomplished. It was thought, that after diastereoselective alkylation and then ester cleavage, a variety of other enantiomerically pure iodoarenes could be achieved easily.



45f

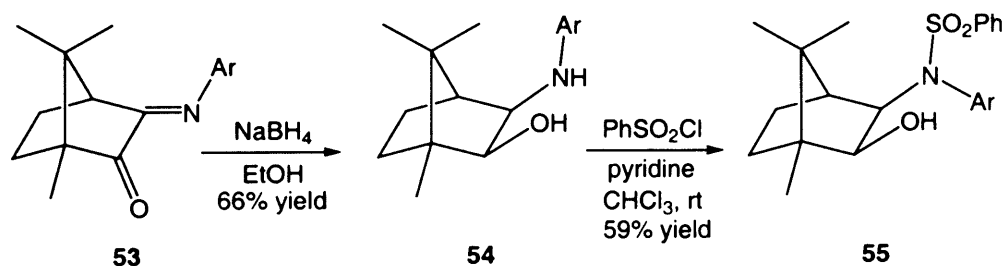


Synthesis of ester **45f** started with the oxidation of (+)-camphor **51** to the respective diketone **52** in good yield using selenium dioxide (Scheme 16). The α -carbon is oxidised probably *via* the enol-derivative of **51** and reaction of the double bond with selenium dioxide to give **52**. Subsequent imination using 3,5-dimethylaniline was conducted without previous purification of camphorquinone **52**. The selectivity of this reaction is due to the steric hindrance of the methyl group next to the carbonyl moiety in **52**. Imine **53** was obtained in good yields (87%).



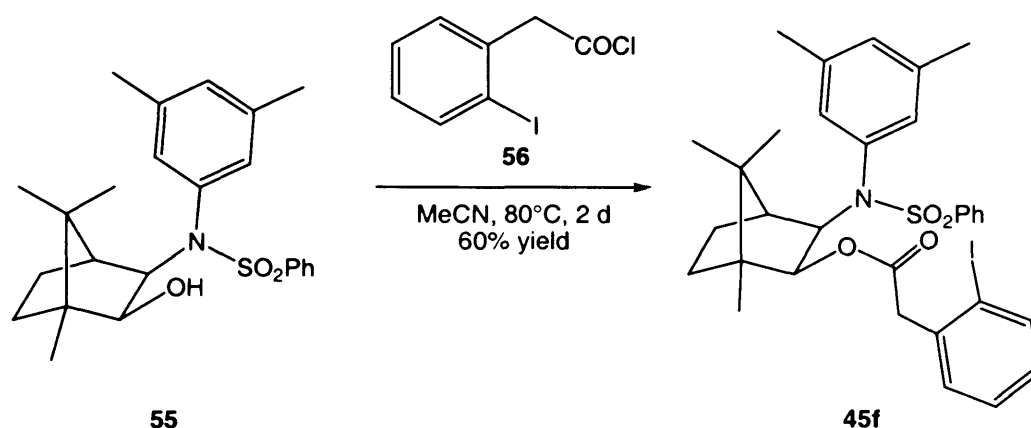
Scheme 16 Synthesis of imine **53**.

Reduction of imine **53** using sodium borohydride resulted in alcohol **54** in moderate yields of 66% (Scheme 17). This reaction proceeds with *endo*-selectivity, possibly due to steric hindrance caused by the configuration of this rigid molecule. The corresponding *exo*-derivative can be obtained by the employment of zinc together with a strong base such as potassium hydroxide followed by alkylation of the amine for the imine moiety and calcium borohydride for the reduction of the carbonyl group.^[31] The final reaction step towards chiral alcohol **55** employed pyridine as a base and benzenesulfonic acid chloride as an electrophile and yielded **55** (59 %).



Scheme 17 Synthesis of alcohol **55**.

(2-Iodophenyl)acetyl chloride **56** was freshly prepared from the respective acid **44** and thionyl chloride by stirring at 100 °C in toluene overnight and was purified by Kugelrohr distillation (115 °C, 10⁻¹ mbar, 79% yield). The esterification of alcohol **55** together with **56** was conducted at 80 °C over two days; after work-up, product **45f** was purified by column chromatography and resulted in 60% yield (Scheme 18).



Scheme 18 Synthesis of ester **45f**.

Since iodoarene **45f** did not show any catalytic activity (see Chapter 4.3), stereoselective alkylation using LICA and LICA/HMPA together with methyl iodide was not done.

After having synthesised a variety of chiral esters, firstly methyl ester **45a** was alkylated in good yield. The resulting enantiomers or diastereoisomers were separated by preparative HPLC on a chiral stationary phase. A variety of sterically increasingly demanding substituents such as a methyl substituent as smallest (**46a**), followed by ethyl (**46b**) and benzyl (**46c**) substituents were introduced. As described in the next chapters, enantioselectivities achieved when methyl esters **46a–c** and **47b–c** were employed in reactions, were highest, when sterically least hindered monosubstituted ester **46a** was used.¹ Introduction of a second bulkier substituent into **46a** did not result in enhanced selectivities in reactions. After determination of the optimal substituent, esters **45b–f** were furnished with one methyl group. Bulkier benzyl ester **45b** was alkylated under similar conditions. However, enantiomers of **46d** could not be separated by preparative HPLC and remained unused. Now looking back, this problem could have been circumvented by synthesis of an ester separable by preparative HPLC, which would be reduced using reducing reagents such as LiAlH₄^[33] or H₂, Pd/C^[34] and then re-esterified to the desired now enantiomerically pure substituted benzyl

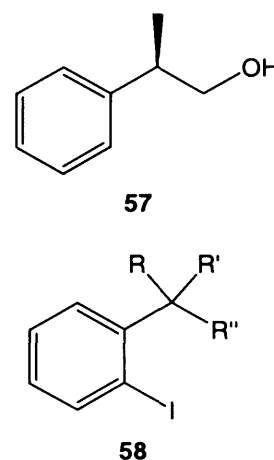
¹ See Chapter 4.3

ester. Time reasons did not allow intensive investigations on that particular problem, since many other promising iodoarenes needed to be investigated. Experiences regarding hydrolysis of esters **45** or **46** will be discussed later. Likewise, esters **45c–e**, which already contain a bulky chiral moiety, were alkylated resulting in diastereomers **46e–g**. These diastereomers were also separated by preparative HPLC; so now very promising iodoarenes furnished with two chiral moieties could be employed.

2.2.5 Manipulation of Esters

In order to proceed the synthesis of iodoarenes **24**, a range of esters **45–47** were attempted to be functionalised to the respective aldehydes, alcohols or carboxylic acids (Table 4). Firstly, when DIBAL-H was employed, starting material **47a** was recovered (entry 1). Then, ester **47a** was stirred in a solution of NaOH (entry 2) or LiOH (entry 3) in a THF/H₂O (1:1) mixture; only starting material was recovered in all cases. Also, TMSCl was used together with NaI in acetonitrile at 45 °C (entry 4), but no reaction took place.^[35] Finally, lithium aluminium hydride in dry THF yielded in the respective de-iodinated alcohol **57** in excellent conversions of 99% (entry 5).

Entry	Reagent	Ester	58-R''	Conversion ^a (%)
1	DIBAL-H	47a	CHO	0
2	NaOH	47a	COOH	0
3	LiOH	47a	COOH	0
4	TMSCl/NaI	45a	COOH	0
5	LiAlH ₄	46a	CH ₂ OH	99
6	LiAlH ₄	46f	CH ₂ OH	99

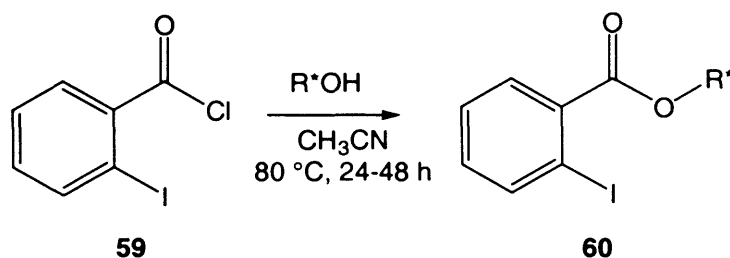


a conversion was determined by ¹H NMR analysis.

Table 4 Attempted manipulation reactions of esters **45–47**.

2.2.6 Synthesis of Precursors of Chiral Five-Membered Ring Iodane Esters

In order to investigate selectivities of esters of the type **45d–f** furnished with a shorter side chain in *ortho*-position to the iodine atom, 2-iodobenzoyl chloride **59** was stirred together with the respective terpene derivatives used in former syntheses (Table 5) in acetonitrile at 80 °C for one to two days. In this way, chiral iodoarenes can conveniently be obtained in a one-step synthesis from commercially available reagents in excellent yields of 88–98%.

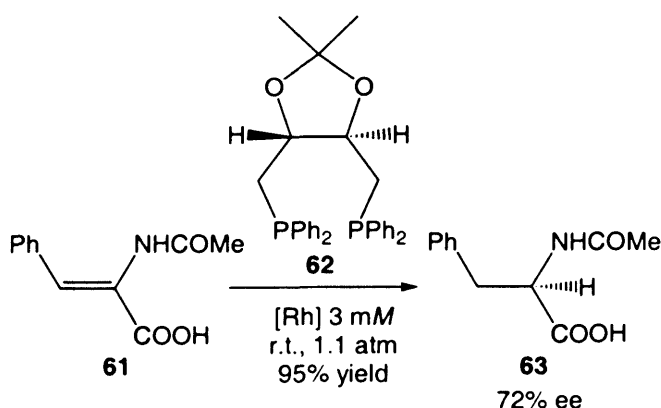


Nr	R ^(*)	Yield %
60a	(–)-Bornyl	94
60b	L-Menthyl	98
60c	(+)-Fenchyl	88

Table 5 Convenient one-step synthesis of chiral iodoarenes **60**.

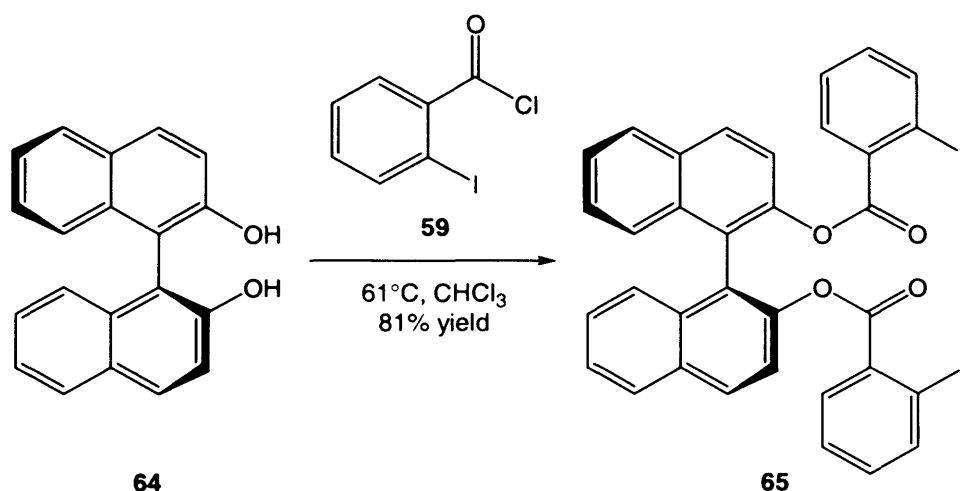
2.2.7 C₂-Symmetric Iodoarenes

One of the first to investigate C₂-symmetric compounds was Kagan and co-workers. After synthesis of ligand **62** its use as catalyst in asymmetric hydrogenation reactions was examined resulting in up to 72% *ee* (Scheme 19).^[36,37]



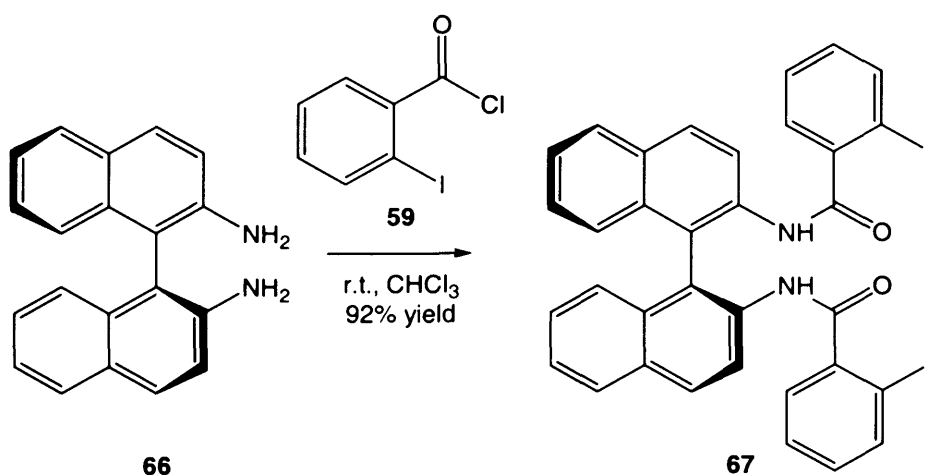
Scheme 19 An example of a C₂-symmetric compound used in enantioselective reactions.

C₂-symmetric iodoarenes were prepared using *S*-(–)-binaphthol and (–)-TADDOL derivatives. Binaphthyl derivatives have been acknowledged to provide highly stereoselective recognition and have been used e.g. for the reduction of prochiral carbonyl compounds.^[38] Ester **65** was synthesised from 2-iodobenzoyl chloride **59** and binaphthol **64** at 61 °C in chloroform overnight resulting in ester **65** in a good yield of 81% (Scheme 20). Both, racemic and enantiomerically pure esters have been synthesised. The enantiomerically pure binaphthyl starting material was highly unpure and could not be purified successfully before the reaction; ester **65** could hardly be purified due to partial decomposition during column chromatography and therefore could not be used for further reactions.



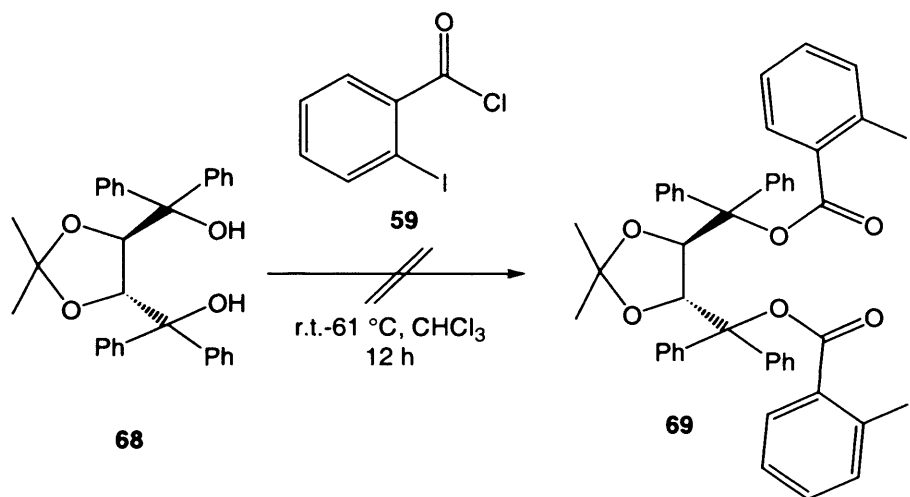
Scheme 20 Synthesis of the C₂-symmetric *S*-(–)-iodoarene **65**.

Since amides form more stable compounds than esters, the respective (*S*)-(–)-binaphthyl amide was synthesised (Scheme 21). Amide **67** was synthesised in the same manner as ester **65** from the corresponding binaphthyl amine **66**; reaction conducted at room temperature resulted in a very good yield of 92%. After purification by column chromatography, amide **67** was used in reactions.



Scheme 21 Synthesis of the amide analogue **67** of C₂-symmetric *S*-(–)-iodoarene **65**.

A bulkier kind of C_2 -symmetric molecule would be achieved by replacing the BINOL moiety by a (–)-TADDOL **68** moiety, a tartaric acid derivative (Scheme 22).^[39] In the past, derivatives of **68** have been used as chiral auxiliaries among others in Grignard-type reactions^[40] or in enantioselective diethylzinc addition to aldehydes.^[41] Compound **68** was thought to be a very promising moiety in iodoarene esters of type **69**. The synthesis was conducted *via* a similar method to that described above, but did not result in the desired product **69**; no further investigations were undertaken.

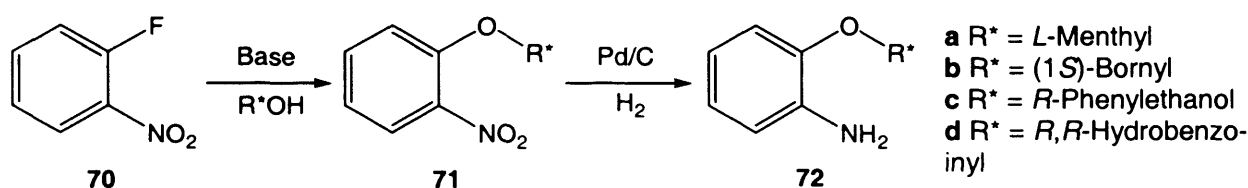


Scheme 22 Attempted synthesis of the C_2 -symmetric (*R,R*)-TADDOL ester **69**.

2.2.8 Synthesis of Chiral Iodoaryl Ethers

Also, iodoaryl ethers furnished with asymmetric centres were synthesised.¹ For this purpose, 1-fluoro-2-nitrobenzene **70** was refluxed together with sodium hydride as base and a terpene alcohol (menthol and borneol) resulting in the respective nitrobenzene ethers **71** in isolated yields up to 92% (Table 6). 1-(*R*)-Phenylethanol and (*R,R*)-hydrobenzoin could not be converted into the desired ether using the same base, but the employment of potassium bis(trimethylsilyl)amine as a base^[42] afforded 1-phenylethylether-2-nitrobenzene **71c** in very good conversions. The transformation of (*R,R*)-hydrobenzoin under similar conditions did not reach full conversion and gave ether **71d** in 37% yields. However, the completion of the synthesis of the respective (*R,R*)-hydrobenzoin iodoaryl ether **72d** was not done.

Nitrobenzene ethers **71** were then reduced to the respective amines using palladium catalyst in hydrogen atmosphere in good yields (93–96%).^[43] In order to optimise the yield of the hydrogenation step, the reaction was conducted in a large flask in order to enhance the reaction surface, resulting in excellent conversions after 4–6 h of reaction time.



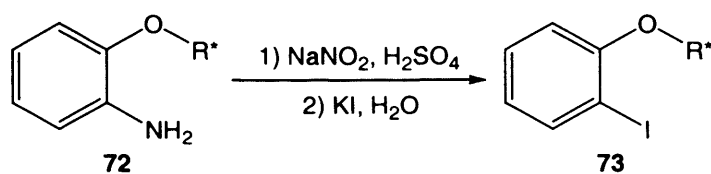
	Yield of 71 (%)	Yield of 72 (%)
a	92	93 ^a
b	90	96 ^a
c	95 ^a	95 ^a
d	37	-

^a yield of crude product

Table 6 Synthesis of chiral aniline derivatives **72**.

The iodination of **72** was carried out under Sandmeyer conditions by diazotation using NaNO₂ and iodination employing potassium iodide (Table 7).^[44,45] Iodoaryl ethers **73** were found to be unstable towards heat but could be obtained in satisfactory yields of crude products of up to 70% when not heated during solvent evaporation. Due to their instability, the crude products were used without purification in reactions.

¹ R. K. Schmidt, E. Holland, student projects summer 2007.



Ether	Yield ^a (%)
73a	54
73b	70
73c	54

a yield of crude product

Table 7 Iodination of amines **72** under Sandmeyer conditions.

2.2.9 Summary

A range of new enantiomerically pure iodine compounds has been synthesised. Iodoarenes furnished with different functional groups such as nitriles, amides, esters and ethers as well as different chiral moieties has been synthesised in good yields.

2.3 Literature

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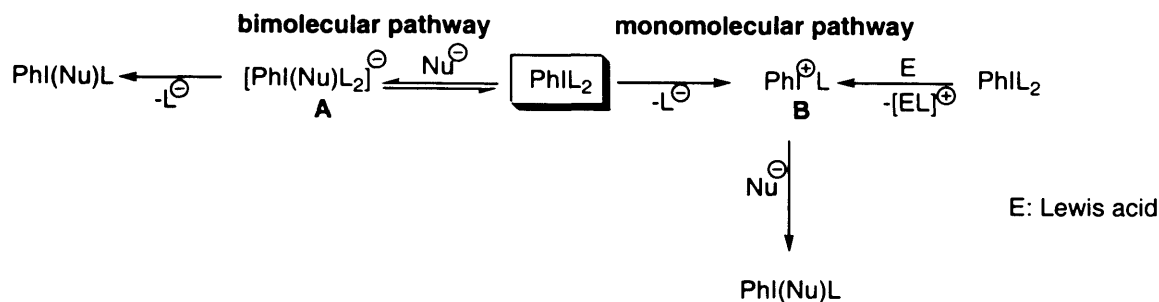
3 Enantiomerically Pure Hypervalent Iodine Compounds

3.1 Introduction

Some description of structural features and examples of reactions of λ^3 - and λ^5 -iodanes has been given in previous chapters. Here, synthetic methods toward these compounds and their employment will be described in more detail as well as their *in situ* formation in catalytic reactions.

3.1.1 λ^3 -Iodanes

Iodanes of type RIL_2 – furnished with two electronegative ligands L – are among the most stable hypervalent iodine compounds. Moiety R is bound by a covalent overlap to the iodine atom, whereas the two ligands L form the 3c-4e bond together with the iodine atom. The fact, that the highest electron density in this bond is located at the ends of the L -I- L triad, makes clear why especially ligands containing electronegative heteroatoms result in more stable iodanes. Compounds of type R_2IL are established for the transfer of one carbon ligand to nucleophiles; they are not good oxidising compounds.^[1] Iodanes containing only carbon ligands are less stable, Ph_3I e.g. decomposes above 0 °C to give biphenyl and iodobenzene. Another possibility are compounds of type IL_3 , in which L can be halogen atoms. The respective iodanes containing bromide or chloride substituents are commercially available and can be used for the halogenation reactions.^[2,3] However, a great range of λ^3 -iodanes are derivatives of iodobenzene and these are the ones discussed in the following. Usually, (dichloriodo)benzene and (diacetoxyiodo)benzene serve as starting material for other λ^3 -iodanes; suitable nucleophiles can be introduced by ligand exchange.^[4] This reaction can proceed *via* a bimolecular (associative) pathway forming a tetracoordinated intermediate **A** or *via* a monomolecular (dissociative) pathway forming an iodonium cation **B** (Scheme 1). The take-up of electrons of the already partially positively charged iodine atom is enhanced by the introduction of electron-withdrawing substituents at the aryl moiety.

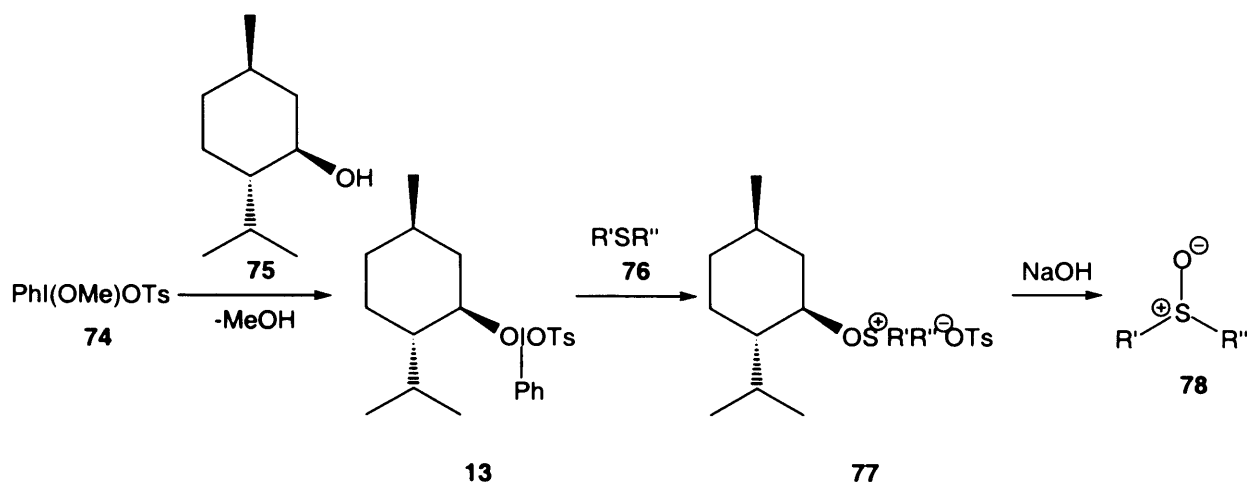


Scheme 1 Different pathways for the ligand exchange of λ^3 -iodanes.

On the other hand, ligand exchange reactions can be enhanced by the use of iodanes with good leaving groups; in this way, e.g. bis(trifluoroacetoxyiodo)benzene is known to be one of the most reactive iodanes.

Iodanes of type R_2IL – diaryliodonium salts – do not possess an onium salt-like structure, but a trigonal-bipyramidal structure with a ligand L (halogen atom, OTs, OCOR, etc) in one, and an aryl group in the other end of the 3c-4e bond.^[5] Usually, onium salts such as ammonium, sulfonium or phosphonium salts have a tetrahedral geometry.^[6] Diaryliodonium salts are less reactive than iodanes and are used in electron transfer reactions and nucleophilic aromatic substitution reactions.

λ^3 -Iodanes containing different heteroatom ligands have been synthesised and employed as oxidants. Many λ^3 -iodanes have oxygen, nitrogen or sulphur ligands. Koser and co-workers synthesised iodanes **13** furnished with chiral moieties such as menthyloxy-ligands quantitatively by stirring [methoxy(tosyloxy)iodo]benzene **74** together with (+)- or (–)-menthol in dichloromethane; compound **13** was employed in the synthesis of enantioenriched sulfoxides **78** with enantiomeric excesses of up to 99% *via* a (menthyloxy)sulfonium tosylate intermediate **77** (Scheme 2).^[7] In this reaction, a electron lone pair of the sulfide attacks the iodine atom, thus replacing the menthoxy group in **13**. In the next step, the menthoxy group can bond to the now positively charged sulphur atom in [sulfonium(tosyloxy)iodo]benzene and form **77**. After hydrolysis with aqueous sodium hydroxide solution, enantioenriched sulfoxide **78** is obtained.

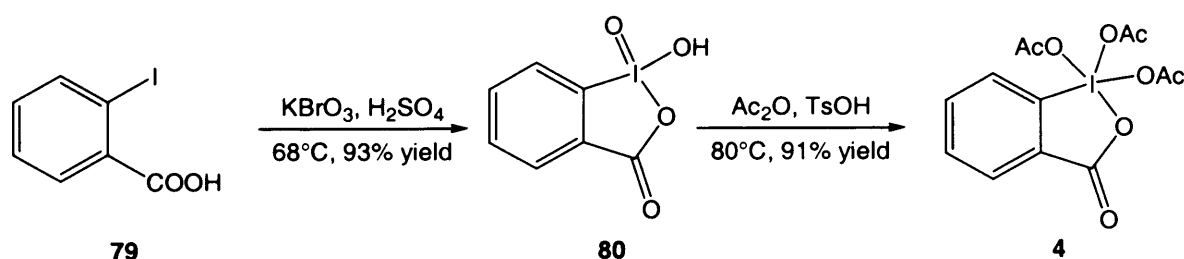


Scheme 2 Ligand exchange and reductive elimination of λ^3 -iodanes and enantioselective oxidation of sulfides.

3.1.2 λ^5 -Iodanes

Pentavalent iodine compounds have proven to be mild oxidising agents. The IO_2^+ -moiety is isoelectronic to ozone and, therefore, reactions employing iodyl compounds proceed in a comparable mechanism. It is reported, that iodylarenes generally are polymeric and can not be dissolved in ordinary solvents. They are thermally stable unless heated in the absence of solvents: melting points usually are explosion points.^[4]

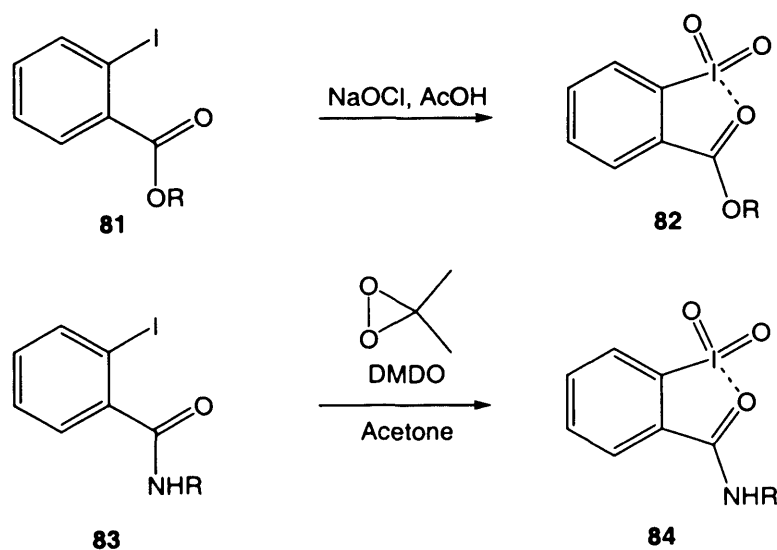
The first iodyl compound, PhIO_2 , was synthesised by Willgerodt in 1900.^[8] Usually, iodylarenes are prepared by treatment of iodoarenes with strong oxidants such as peracetic acid,^[9] sodium hypochlorite,^[10] potassium peroxymonosulfate^[11-13] or diacetyl peroxide.^[14] The well-established Dess-Martin-Periodinane (**4**) was synthesised in 1983 from *o*-iodoxybenzoic acid **80** (IBX) by boiling in acetic anhydride together with an acid such as acetic acid or *p*-toluene sulfonic acid;^[15-19] IBX **80** was obtained by oxidation of *o*-iodobenzoic acid **79** with potassium bromate in sulfuric acid,^[16,19,20] peracetic acid or aqueous sodium hypochlorite (Scheme 3).^[10]



Scheme 3 Synthetic route towards the Dess-Martin-Periodinane **4**.

The advantage of DMP **4** is the enhanced stability as well as safety since iodoxybenzoic acid **80** was experienced to be explosive under excessive heating or impact.^[21] On the other hand, Dess and Martin assumed this to be caused by the presence of bromate or other impurities.^[19] Cyclic iodylarenes possess an enhanced stability, because the pentavalent iodine atom is part of a five-membered ring; noncyclic iodylarenes have been reported to have explosive properties.^[22-26]

Some years ago, the synthesis and employment of IBX esters **82**^[27] and IBX amides **84**^[28] has been reported (Scheme 4). These esters belong to a new class of pentavalent iodine compounds with a pseudobenziodoxole structure and have been employed successfully in oxidising alcohols to the respective aldehydes or ketones in excellent yields of 95–100%.^[29] The ester moiety in **81** can be e.g. chiral moieties derived from menthol or borneol. A variety of alcohols was oxidised by esters **82** in presence of TFA, KBr or BF₃-etherate. Benzaldehyde was obtained when benzyl alcohol was stirred together with KBr as catalyst in chloroform at 50 °C.^[30] Amides **84** oxidised successfully primary and secondary alcohols to the corresponding aldehydes and ketones without the presence of an acid, in contrast to non-cyclic iodylarenes such as PhIO₂. Iodylbenzene only reacts after appropriate activation such as stirring in DMSO, since the strong intermolecular bonding between the iodine atom and an oxygen atom uses the coordination site at the iodine atom necessary for reactions.^[31-34] When R was CH(CH₂Ph)CO₂CH₃ thus forming a chiral amide **84**, the remaining alcohol showed some enantioenrichment of 9%, when 1-phenylethanol was oxidised in CDCl₃ at room temperature over a time period of 18 hours.^[28]

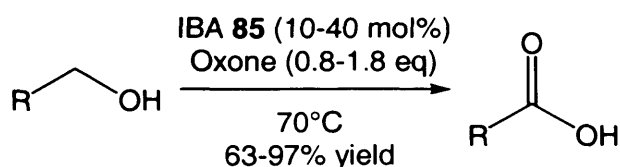
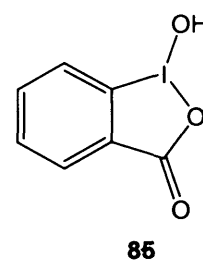


Scheme 4 Synthesis of IBX-esters **82** and IBX-amides **84**.

3.1.3 Catalytic Reactions

Recently, reactions using only catalytic amounts of (hypervalent) iodoarenes have been developed.^[35-37] Hypervalent iodine compounds are formed *in situ* by stoichiometric oxidants; after ligand exchange and reductive elimination the iodoarene can be re-oxidised for further reaction. Reactions, where λ^3 -iodanes are formed *in situ* from iodoarenes will be discussed in chapter 4 in more detail, for now the emphasis will lie on λ^5 -iodanes.

Iodine(V) reagents can be obtained from the corresponding iodine(I) or iodine(III) compounds *in situ*. One example is the catalytic one-step oxidation of aliphatic primary alcohols to the respective carboxylic acid using IBA **85** as catalyst and oxone as stoichiometric oxidant, thus forming IBX **80** *in situ*, only benzyl alcohol resulted in the respective aldehyde without further oxidation (Scheme 5). Usually, aqueous solvent systems are used such as acetonitrile/water^[38] or ethyl acetate/water together with a phase-transfer catalyst ($n\text{Bu}_4\text{NHSO}_4$).^[39]



Scheme 5 Catalytic oxidation of primary alcohols using IBA **85**.

Also, other catalytic systems are reported using elemental oxygen, NO and HBr as oxidants in order to generate PhIO_2 from $\text{PhI}(\text{OH})_2$ ^[40] or λ^3 -iodane catalysed reactions mediated by TEMPO and KNO_2 ;^[41] both methods forming ketones from alcohols.

3.1.4 Task

A range of iodoarenes has been synthesised within this project. These compounds were to be oxidised to the corresponding hypervalent compounds using a range of suitable oxidants in order to obtain both, λ^3 - and λ^5 -hypervalent iodine compounds. The hypervalent iodine compounds achieved in this way were then to be employed in oxidation or functionalisation reactions, depending on the nature of iodanes formed.

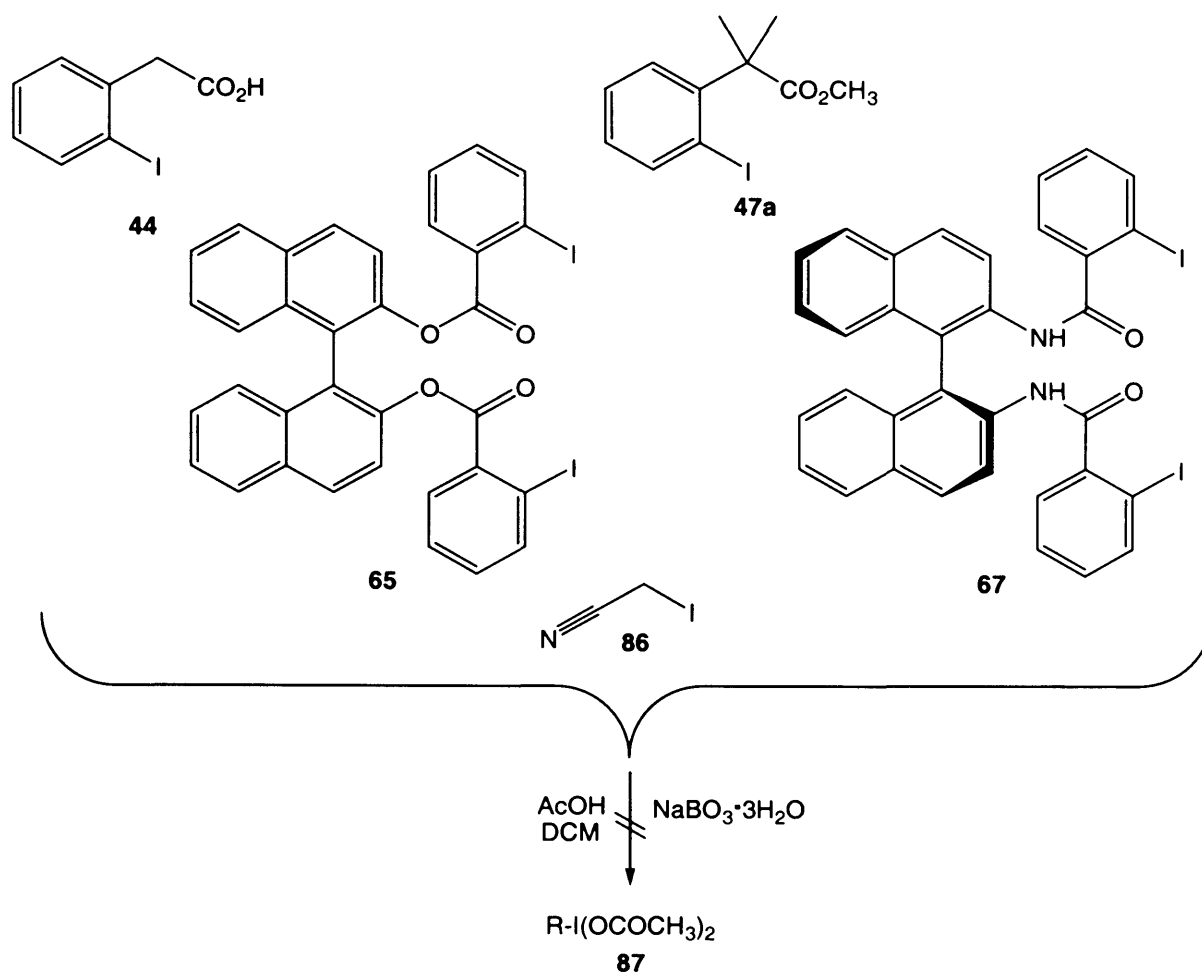
3.2 Results and Discussion

A range of different oxidation methods was used in order to prepare hypervalent iodine compounds from the corresponding iodoarenes synthesised during this project in order to achieve both, λ^3 - and λ^5 -iodanes.

3.2.1 λ^3 -Iodanes

3.2.1.1 Oxidation Using Sodium Perborate Trihydrate

McKillop and co-workers have synthesised (diacetoxyiodo)benzene from iodobenzene using sodium perborate trihydrate in acetic acid at 40–45 °C.^[42] The same oxidising system was applied to iodoarenes synthesised during this project (Scheme 6). A small amount of dichloromethane was added to the reaction mixtures in order to dissolve the iodoarenes. During the work-up, different drying agents were used such as MgSO_4 , Na_2SO_4 or molecular sieves (4 Å), in order to avoid possible decomposition of the product **87**. When ester **65** was attempted to be oxidised in this manner, the reaction mixture was heated slowly from 40 °C to 100 °C over a time period of two days. Although TLC indicated the possible formation of a product, only starting material was recovered after work-up. The same phenomenon was observed for the attempted oxidation of all other iodoarenes shown in Scheme 6 such as amide **67**, disubstituted methylester **47a**, iodoacetonitrile **86** and (2-iodophenyl)acetic acid **44**.



Scheme 6 Attempted oxidation toward λ^3 -iodanes **87** using sodium perborate trihydrate.

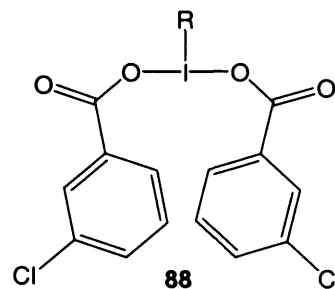
3.2.1.2 Oxidation Using Peracetic Acid

Peracetic acid was also used as oxidising agent for the synthesis of (diacetoxyiodo)benzene derivatives **87**. For this purpose, either commercially available peracetic acid was used (**Method A**) or it was generated from hydrogen peroxide and acetic anhydride *prior* to oxidation reactions (**Method B**).^[43,44] Firstly, binaphthyl ester **65** was attempted to be oxidised according to Method A. Ester **65** was stirred in a solution of peracetic acid and a small amount of dichloromethane under stepwise heating (40–100 °C) over a time period of two days, but TLC analysis showed the possible formation of an oxidised product as well as decomposition of **65**. After work-up, no oxidised **65** was detected. When disubstituted ester **47a** was stirred in peracetic acid (Method A) at 45 °C for four days, mainly starting material was observed from TLC, but also some possible development of the oxidised product; however, only starting material was recovered. Also, when **47a** was attempted to be oxidised under conditions of Method B at 40 °C for three hours, only starting material was detected by NMR analysis after work-up. Similar results were observed from the

reaction of **44** and iodoacetonitrile **86** under conditions of method A. Binaphthyl amide **67** was employed according to method B and was stirred at room temperature for two days; TLC analysis showed the possible generation of oxidised product, but could not be found from NMR analysis after work-up.

3.2.1.3 Oxidation Using *m*CPBA

Morris and co-workers obtained the respective DIB-derivative **88** by stirring iodine compounds in dichloromethane together with *m*CPBA at room temperature.^[45] In this prospect, some iodoarenes were treated in this manner. Binaphthyl ester **65** was treated in this manner, but only unidentified aromatic fragments were detected by NMR analysis; similar results were observed from the oxidation reaction of disubstituted ester **47a**.



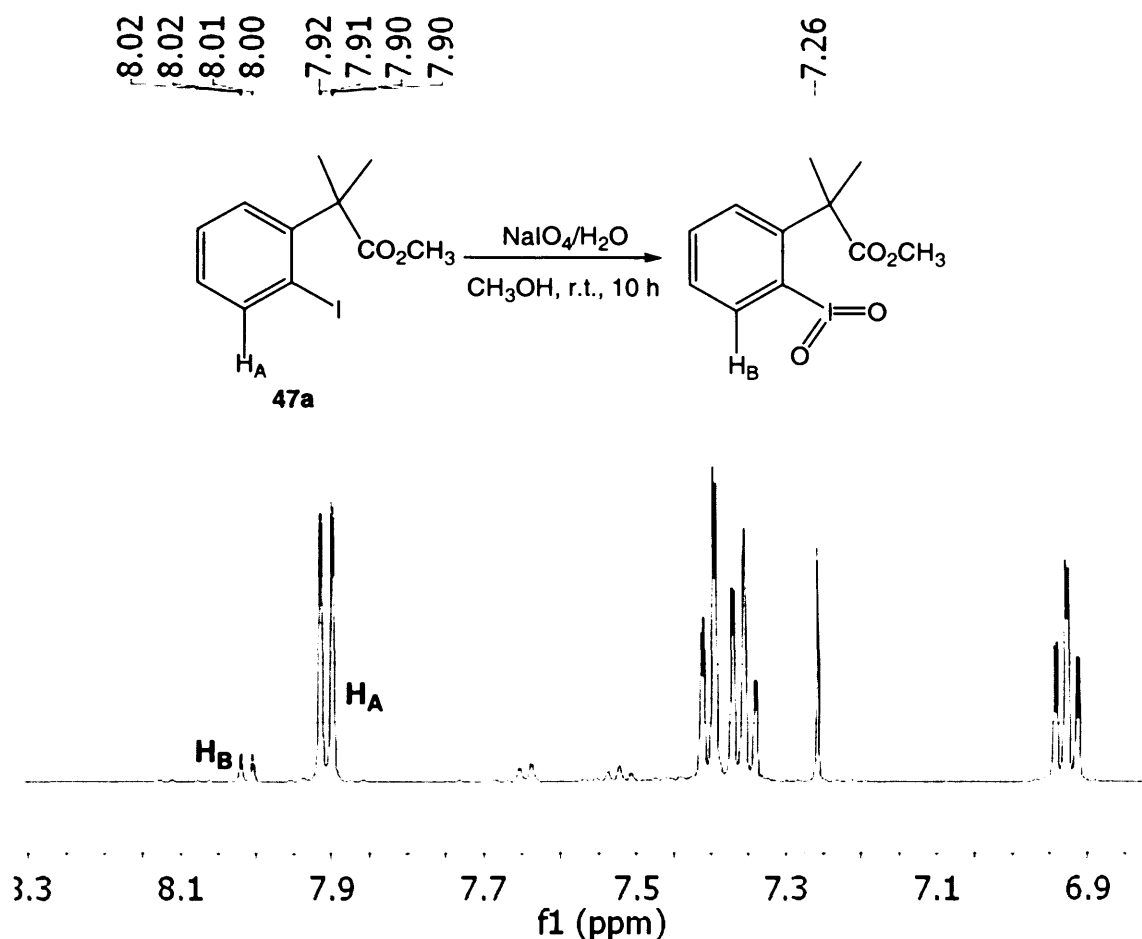
3.2.2 λ^5 -Iodanes

Usually, iodyl compounds $R\text{-IO}_2$ are prepared by direct oxidation of iodoarenes using strong oxidants such as sodium hypochlorite, dimethyldioxirane (DMDO), sodium periodate and oxone. It is assumed, that iodoarenes are oxidised to the corresponding iodosylarenes, which then disproportionate to iodylarenes either at room temperature or by heating.^[46-49] In most cases, the product will precipitate from the reaction mixture and is purified by recrystallisation. Experiences in the past have shown, that dry iodyl compounds might explode upon heating or impact and therefore have to be handled with care. X-ray structural analysis was done from IBX **80**, which exhibited a strong interaction between the iodine atom and the oxygen atom of the acid moiety, thus forming a cyclic structure.^[50]

3.2.2.1 Oxidation Using Sodium Periodate

Kazmierczak and co-workers have developed a synthetic method towards iodyl compounds using two equivalents of sodium periodate in water under reflux in good yields up to 91%.^[46] This method was tested on disubstituted ester **47a**. Compound **47a** was stirred under the above described conditions at a temperature range from room temperature to reflux for two days. After work-up, NMR analysis showed the possible development of traces of the

desired iodane (Scheme 7), but because of the poor conversion of 7% of this reaction, no further investigations were done at this time. Based on ^1H NMR analytic observations described later in this chapter, it is determined, that the aromatic proton H_B in the pseudo-cyclic iodyl ester in the *ortho*-position to the iodine atom possesses a shift to above 8.0 ppm.



Scheme 7 Partial ^1H NMR spectrum of the crude reaction mixture of the oxidation reaction using sodium periodate (only aromatic area).

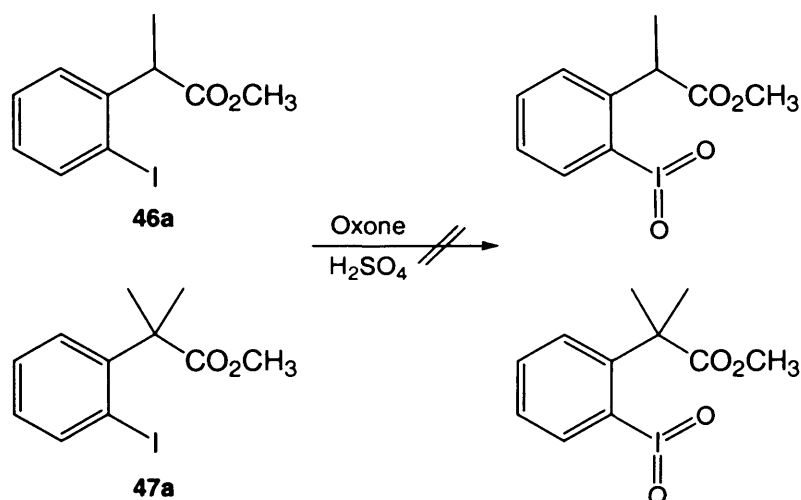
3.2.2.2 Oxidation Using Potassium Bromate

Another synthetic pathway towards iodyl compounds is the mixture of iodoarenes with potassium bromate and sulfuric acid under heating up to 68 °C for about four hours.^[51] This step is described as the first synthetic step towards DMP from 2-iodobenzoic acid. Two iodoarenes synthesised during this project have been exposed to these conditions. Firstly, binaphthyl ester **65** was employed; after work-up, only starting material was recovered. Then,

disubstituted ester **47a** was attempted to be oxidised under these conditions, but by NMR analysis only starting material was observed.

3.2.2.3 Oxidation Using Oxone

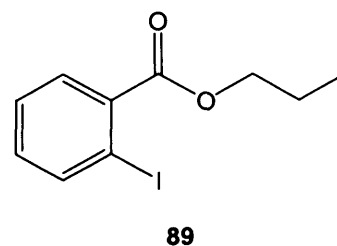
2-Iodobenzoic acid **79** can not only be oxidised to IBX **80** by potassium bromate, which has to be handled with special care, since potassium bromate is carcinogenic, but also by using oxone, a mixture of $\text{KHSO}_3/\text{KHSO}_4$ and K_2SO_4 .^[52] Acid **79** was stirred together with 1.3 equivalents of oxone in water at 70°C for three hours resulting in up to 81% yield of **80**. Mono- and disubstituted methyl ester **46a** (entry 1) and **47a** (entry 2) have been attempted to be oxidised using oxone under these conditions (Scheme 8). In both reactions, only starting material was detected after work-up.



Scheme 8 Iodoarenes attempted to be oxidised by oxone/sulphuric acid.

3.2.2.4 Oxidation Using NaOCl

Zhdankin and co-workers synthesised esters of 2-iodobenzoic acid **79** using sodium hypochlorite together with acetic acid in dichloromethane. After successful oxidation of **89**¹ under these conditions, a wider range of iodoarenes was employed (Table 1, entry 1). The aromatic proton in *ortho* position to the iodine atom of **90** show a shift above 8 ppm in the ¹H NMR spectrum, the characteristic carbon frequency of the carbon atom attached to the iodine atom of 90–100 ppm in the ¹³C NMR was



¹ Ester **89** was synthesised by L. Tröndlin, Summer Project 2005.

not detected, this fact being another indication of the formation of an oxidised species of **89** (Scheme 9). However, the carbon frequency of the corresponding carbon atom of the hypervalent compound could not be detected by the employment of 256 scans. An additional carbon spectrum should have been run using 1024 scans. Also, acid **44** was employed as starting material, but could not be oxidised under these conditions; starting material was recovered (entry 2). Menthyl ester **46f** furnished with two chiral moieties could not be oxidised with this method, only starting material was recovered (entry 3). Disubstituted methyl ester **47a** was also employed in this reaction series, but only starting material was observed by NMR analysis.

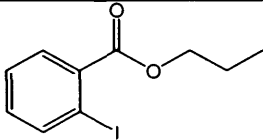
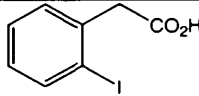
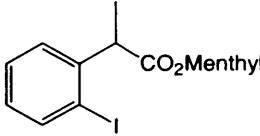
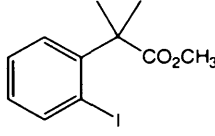
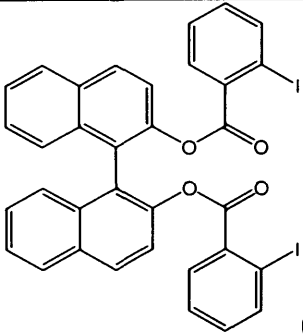
Entry	R-I	Yield [%]
1	 89	66
2	 44	-
3	 <i>rac</i> - 46f	-
4	 47a	-
5	 65	-

Table 1 (continued on next page) Oxidation reactions of iodoarenes using sodium hypochlorite.

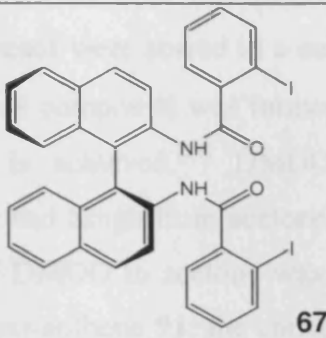
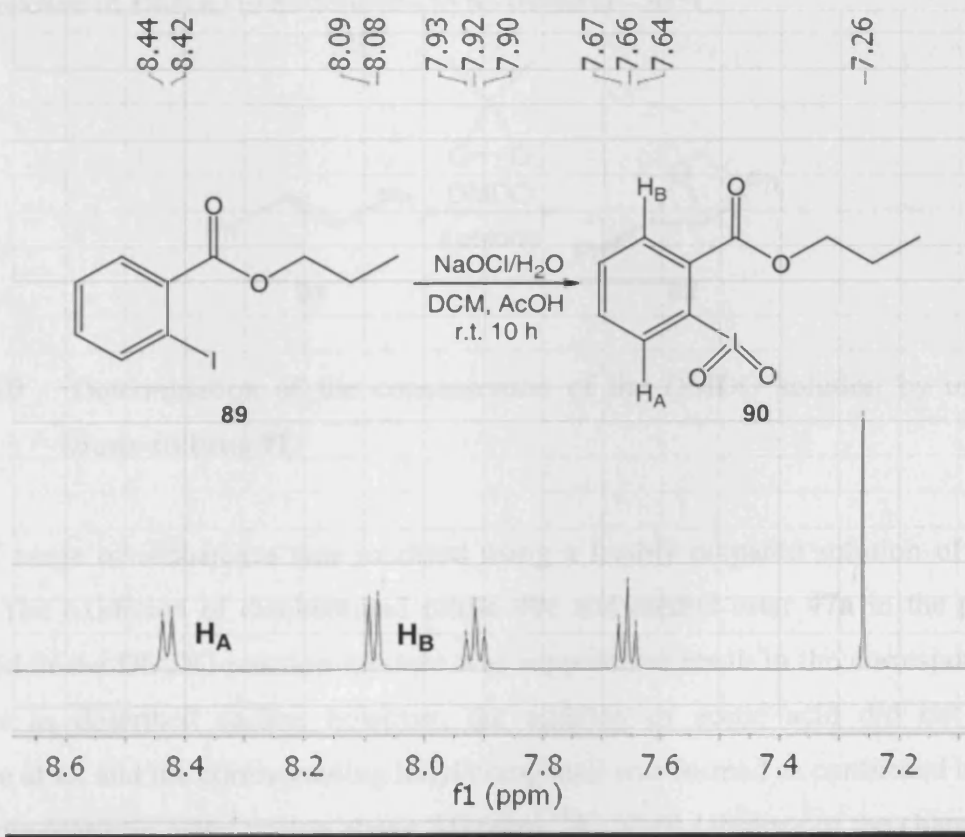
Entry	R-I	Yield [%]
6		-

Table 1 (continued) Oxidation reactions of iodoarenes using sodium hypochlorite.

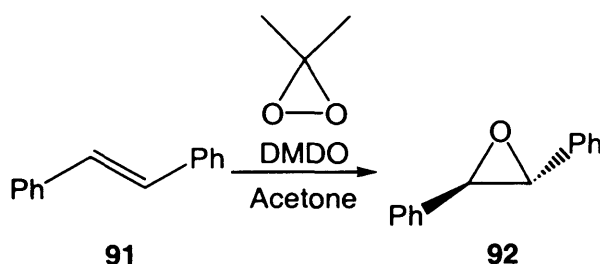
Also, binaphthyl ester **65** and amide **67** were used as starting materials; for **65** some unidentified aromatic fragments were detected by ^1H NMR analysis (entry 5), whereas for **67** starting material was recovered (entry 6).



Scheme 9 ^1H NMR shift of the aromatic protons of iodol derivative **90** to 7.6–8.5 ppm shown.

3.2.2.5 Oxidation Using DMDO

Dimethyldioxirane (DMDO) has been used in the past to oxidise iodoarenes to λ^3 - as well as λ^5 -iodanes: when iodoarenes were stirred in a solution of DMDO in acetone at 0–20 °C, the respective iodyl or iodosyl compound was formed. In the presence of acetic acid, the corresponding DIB derivative is achieved.^[53] DMDO was synthesised according to a procedure developed by Murray and Singh from acetone, oxone, NaHCO_3 and water.^[54] The concentration of the solution of DMDO in acetone was determined by the reaction of 1 ml DMDO solution with 30 mg *trans*-stilbene **91**; the conversion determined from the ^1H NMR of the crude reaction mixture of this reaction gave the concentration of the solution (Scheme 10). Concentrations of DMDO solutions are generally low, 0.07–0.09 M are reported. This is probably due to the high volatility of the product. In order to achieve optimum yields, extra care and constant vigilance has to be taken with regards to the sealing of the reaction apparatus as well as to efficient stirring of the reaction mixture using an overhead stirrer. The product mixture of DMDO in acetone has to be stored at –20 °C.

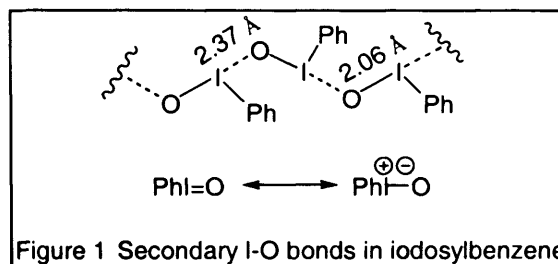


Scheme 10 Determination of the concentration of the DMDO solution by oxidation of *trans*-stilbene **91**.

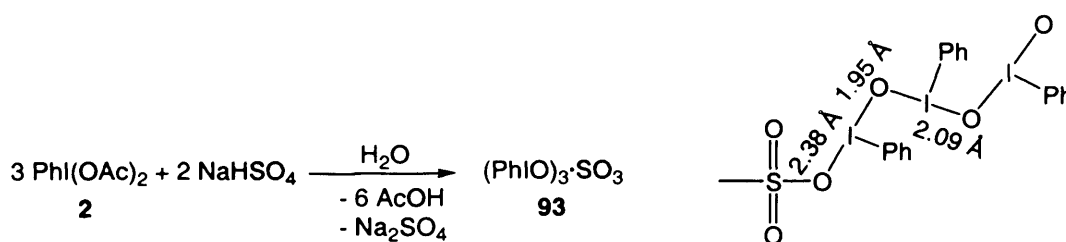
A range of iodoarenes was oxidised using a freshly prepared solution of DMDO in acetone. The oxidation of disubstituted nitrile **40c** and methyl ester **47a** in the presence of acetic acid in the DMDO-reaction mixture was supposed to result in the corresponding DIB-derivative as described earlier; however, the addition of acetic acid did not make any difference at all and the corresponding iodyl compound was formed as confirmed by ^1H NMR (shift of the aromatic *ortho*-proton above 8.0 ppm), ^{13}C NMR (absence of the characteristic C–I peak around 95 ppm), IR (strong peak at 769 cm^{-1}) and mass spectrometry; therefore, all reactions were performed without the addition of acetic acid (Table 2). After reaction completion, the solvent was evaporated to give white solids; remains of starting materials were collected by washing with diethyl ether. Yields achieved ranged from promising 44–

99%. Not all iodoxy derivatives could be fully characterised due to sometimes very small amounts of iodoarenes used and not achieving full reaction conversion or also due to the possibility of decomposition of the iodoxy compounds.

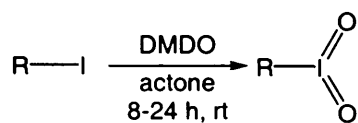
The solubility properties of hypervalent iodine compounds has generally been found to be low in many organic solvents. The analysis of the crystal structures of iodosyl and iodyl compounds can explain their poor solubility properties, which



are caused by strong secondary I-O bonds. The effects of the latter have been investigated thoroughly in the past.^[55] The structure of iodosylbenzene e.g. is built by monomeric units of PhIO, which are linked by intermolecular I...O secondary bonds (Figure 1), thus forcing iodosylbenzene into the form of a zig-zag polymer and making the compound insoluble to many commonly used solvents. The secondary PhI...O bond (2.37 Å) is markedly longer than the polarised PhI⁺-O⁻ bond (2.06 Å, actually a double bond, formally).^[56] Recently, Zhdankin and co-workers developed a stable, water-soluble and non-hygroscopic oligomeric iodosylbenzene sulfate (PhIO)₃·SO₃ by treatment of (diacetoxyiodo)benzene with one equivalent of NaHSO₄ in water.^[57] Iodosylbenzene **93** also possesses a zig-zag structure (Scheme 11) with the I-O bond (1.95 Å) shorter than the SO₂-O-I bond (2.38 Å) and the PhI-O-I bond (2.09 Å). Compound **93** was employed in a range of oxidation reactions.



The solubility of the iodyl compounds **94–98** is dependent on structural features: methyl esters with only one or no substituent did not dissolve in solvents other than DMSO (entries 2, 5–7), whereas esters and nitriles with two or bulkier alkyl substituents as well as all iodoarenes furnished with a terpene moiety were easily dissolved in chloroform or dichloromethane and therefore offer the possibility of mild (and more enantioselective) reaction conditions when used as oxidising reagents.

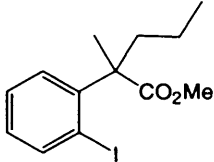
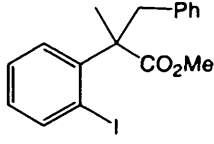
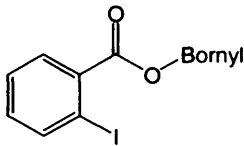
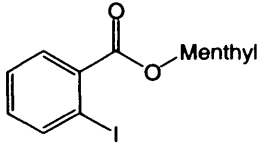
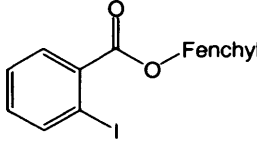


Entry	R-I	R-IO ₂	NMR Solvent	Yield [%]
1	40c	94a	CDCl ₃	71
2	45a	95a	d ⁶ -DMSO	44
3	45c	95c	CDCl ₃	71 ^a
4	45d	95d	CDCl ₃	82 ^a
5	46a	96a	d ⁶ -DMSO	67
6	46b	96b	d ⁶ -DMSO	63
7	46c	96c	d ⁶ -DMSO	51
8	(2S)-46f	(2S)-96f	CDCl ₃	75 ^a
9	(2R)-46f	(2R)-96f	CDCl ₃	46 ^a
10	47a	97a	CDCl ₃	74

^a conversion (determined by ¹H NMR analysis of the crude reaction mixture).

Table 2 (continued on next page)

Synthesis of iodylarenes using DMDO.

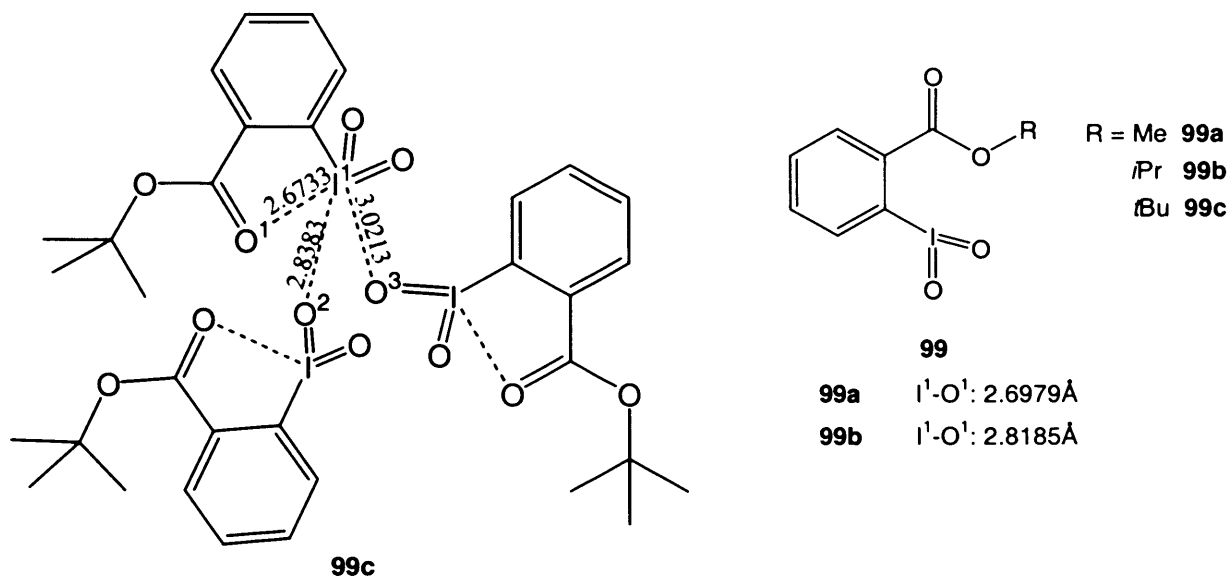
Entry	R-I	R-IO ₂	Solvent	Yield [%]
11	 47b	97b	CDCl ₃	98
12	 47c	97c	CDCl ₃	92
13	 60a	98a	CDCl ₃	54
14	 60b	98b	CDCl ₃	64
15	 60c	98c	CDCl ₃	99

a determined by ¹H NMR analysis of the crude reaction mixture.

Table 2 (continued) Synthesis of iodylarenes using DMDO.

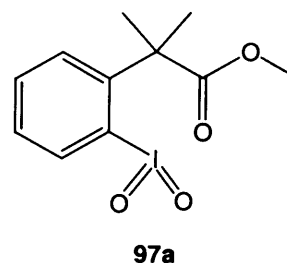
Recently, Zhdankin and co-workers synthesised a range of 2-iodoxybenzoate esters.^[27] These IBX-esters were employed as oxidants for the chemoselective oxidation of sulfides to sulfoxides; no other sensitive functionalities in the sulfides are effected.^[58] In all esters, strong intramolecular interaction of the iodine atom and the oxygen atom of the ester group has been found (Scheme 12). Also, strong secondary I⁺⋯O bonding interactions have been detected. Ester **99a** provided a crystal structure only from DMSO. In this crystal structure, not only the secondary interaction between the iodine atom and the ester oxygen has been found, but also bonding to neighbouring molecules; however, even though a dimeric structure was confirmed, no repeating polymeric interactions have been found. One coordination site of the iodine atom is linked to an oxygen of a DMSO molecule. The structure of **99b** shows not only an interaction between the iodine atom and the ester oxygen but both strong and weak secondary interaction between neighbouring molecules, thus forming a polymeric pattern. The analysis of **99c** showed a centrosymmetric composition of four molecules with secondary I⁺⋯O bonding

interactions; however, unlike observed in **99b**, no additional interactions have been found to connect these tetramers into a polymeric structure.



Scheme 12 Secondary bonding in non-polymeric IBX-ester **99c**.

A crystal structure was obtained from dimethyl-substituted iodylarene **99a** (Figure 2). For detailed data see the Appendix. A similar distance has been found between the iodine atom and the ester oxygen (2.611–2.933 Å). Also, intermolecular secondary I[⋯]O bonding interactions have been detected. The interaction distance from the iodine atom to iodyl oxygen atoms of neighbouring molecules has been found to range from 2.654–3.100 Å. The angle of the 3c4e-bond of O¹⁰-I³-O⁹ has been found to be 101.5(2)°.



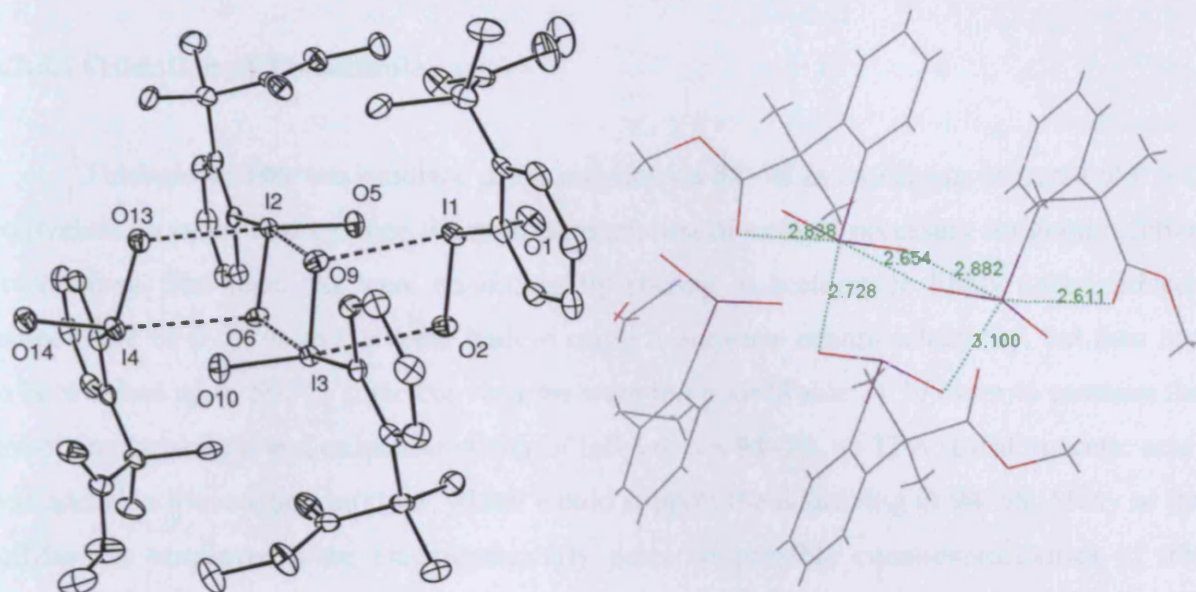


Figure 2 Secondary bonding in iodyl ester **97a**; crystal data are listed in the Appendix.

Generally, it can be said that the bonding features discovered in **97a** are very similar to the ones obtained from the IBX-esters shown above. The distances of the interaction of the iodine atom to the ester oxygen range in similar values to compounds **99a–c** as well as the intermolecular interaction of the iodine atom and the iodyl-oxygen atoms of neighbouring molecules. Likewise, **97a** can be dissolved in commonly used solvents such as CH_2Cl_2 and CHCl_3 .

Iodyl compounds **94–98** generally are stable at room temperature and can be stored for more than one year. Unlike DMP or IBX, iodyl compounds **94–98** have not been found to be explosive, neither when scratched with a spatula nor on impact. When heated above $150\text{ }^\circ\text{C}$, combustion has been observed for some iodylarenes, but in most cases only melting or degradation under discolouration has been observed.

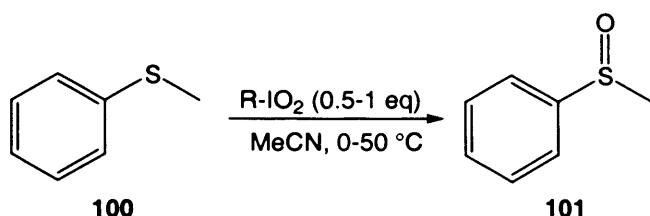
3.2.3 Reactions of Iodoxyarenes

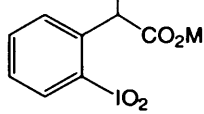
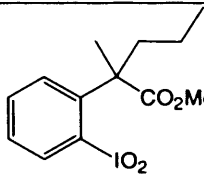
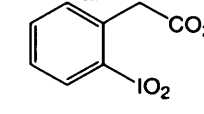
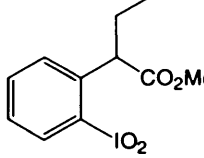
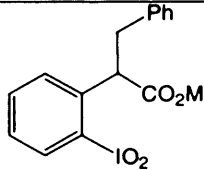
3.2.3.1 Oxidation of Thioanisole

Thioanisole **100** was oxidised using iodylarenes **94–98** as oxidant in amounts of 0.5–1 equivalent, in order to determine the minimum amount of oxidant necessary for good reaction conversions. The reactions were conducted by stirring in acetonitrile firstly under reduced temperature of 0 °C in an ice/water bath in order to improve enantioselectivity, but then had to be warmed up to 50 °C, since conversions were too poor (Table 3). In order to examine the dissolving behaviour and oxidation ability of iodylarenes **94–98**, no TFA (trifluoroacetic acid) was added to the reaction mixture, which would support the dissolving of **94–98**. Many of the iodylarenes employed were enantiomerically pure, so possible enantioselectivities in this reaction could be determined. When the crude reaction mixtures were analysed on HPLC, in some cases no peaks related to product **101** were observed, even though NMR analysis proved the development of sulfoxide **101** – a phenomenon, which can not be explained at this point and would need further investigation. In other cases, the sulfoxide peaks were overlaid by impurities, which could not be removed by preparative TLC. Only two reactions could be analysed by HPLC (entries 4, 8) and showed only very poor enantioselectivities of up to 3% *ee*.

Firstly, two reactions were conducted using 1 equivalent of mono- and disubstituted methyl esters (–)-**96a** and (+)-**97b** (entries 1,2), resulting in excellent conversions of 99%. For the following reactions, the amount of oxidant was reduced: 0.8 equivalent of achiral ester **95a** also resulted in very good conversion of 99% (entry 3), followed by the use of 0.7 equivalent, resulting in promising 19–99% conversion (entries 4–9). Monosubstituted methyl esters (+)-**96b** and (–)-**96c** resulted in good conversions of 94% and 59% (entries 4,5), the difference of the conversion was even higher, when terpene esters with a shorter side chain were used; 99% were achieved using the bornylester **98a** (entry 6), whereas only 19% were observed from the use of the respective fenchylester **98c** (entry 7). It is not believed, that the small configurational difference between these two compounds explains this phenomenon and the reactions should be repeated. Also, esters furnished with longer side chains in *ortho* position to the iodine atom were employed; menthyl ester **95d** achieved very good conversions of 99% (entry 8) and methyl-substituted menthyl ester (2*S*)-**96f** resulted in moderate 68% conversion (entry 9). Then, the use of only 0.5 equivalent of oxidant was tested. Methylated ester (+)-**96a** achieved moderate 57% conversion (entry 10), whereas

bornylester **95c** only resulted in 16% (entry 11). Only methyl-substituted menthylester (2*R*)-**96f** gave excellent conversions of 99% (entry 12). The employment of one equivalent of FIBX² **102** resulted in excellent conversions of 99% and 90% yield (entry 13).^[59] FIBX **102** was synthesised by treatment of FIBA with potassium bromate in dilute sulfuric acid. Basically, the fluorine-containing hypervalent iodine compounds were synthesised in the same manner as the corresponding non-fluorine containing compounds (IBX from IBA).^[59]



Entry	R-IO ₂	eq of R-IO ₂	Conversion ^a of 100 [%]	ee [%]
1	 (-)- 96a	1	99	N.P.
2	 (+)- 97b	1	99	N.P.
3	 95a	0.8	99	-
4	 (+)- 96b	0.7	94	N.P.
5	 (-)- 96c	0.7	59	I.

^a determined by ¹H NMR analysis of the crude reaction mixture.

^b isolated yield.

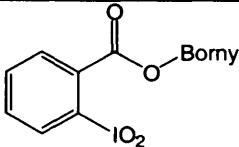
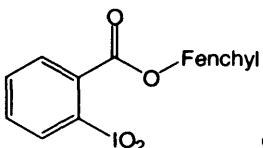
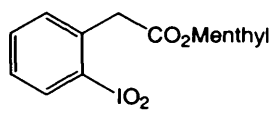
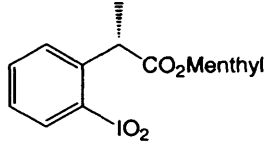
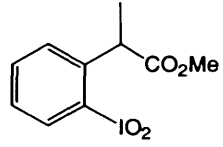
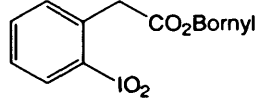
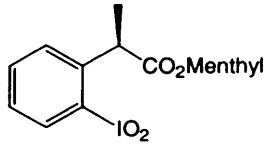
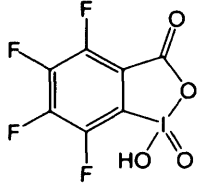
N.P. no product peaks seen on HPLC.

I. impurities overlay product peaks on HPLC.

Table 3 (continued on next page)

Oxidation of thioanisole **100** using novel iodylarenes.

² synthesised by Dr. R.D. Richardson.

Entry	R-IO ₂	eq of R-IO ₂	Conversion ^a of 100 [%]	ee [%]
6	 98a	0.7	99	0
7	 98c	0.7	19	I.
8	 95d	0.7	99	I.
9	 (2S)-96f	0.7	68	N.P.
10	 (+)-96a	0.5	57	N.P.
11	 95c	0.5	16	3
12	 (2R)-96f	0.5	99	N.P.
13	 102	1	99 (90) ^b	-

^a determined by ¹H NMR analysis of the crude reaction mixture.
^b isolated yield.
N.P. no product peaks seen on HPLC.
I. impurities overlay product peaks on HPLC.

Table 3 (continued) Oxidation of thioanisole **100** using novel iodylarenes.

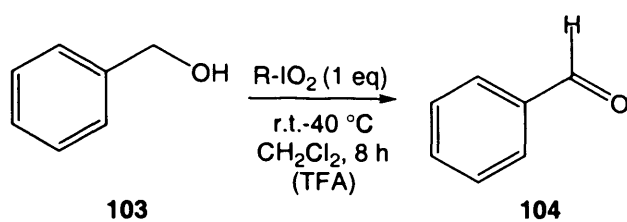
From this reaction series, some conclusions can be drawn. When 1 equivalent of oxidant is used, usually excellent conversions are achieved; the use of fewer amounts of oxidant gave mixed results with no exact trends observed. When 0.7 equivalents were used, already small structural differences seem to result in dramatic change of conversions, e.g. the

introduction of a methyl group in the *ortho* side chain resulted in a gap of 31%, a similar trend – but in opposite direction – was observed from the use of only 0.5 equivalent. Further investigations are of need. Also, reactions should be repeated using TFA in order to improve the solubility of oxidants **94–98**, possibly resulting in milder reaction conditions and improved enantioselectivities.

3.2.3.2 Oxidation of a Primary Alcohol

IBX was employed in the oxidation of primary and secondary alcohols at room temperature in DMSO by Frigerio and Santagostino.^[60] In order to investigate the oxidation properties of iodyl arenes synthesised during this work, a range of compounds **94–98** was employed as oxidant in the oxidation of benzyl alcohol **103** (Table 4). All reactions were conducted in dichloromethane or acetonitrile at room temperature with one equivalent of iodyl compounds, depending on the reaction progress observed by TLC. When iodyl compounds **94–98** was not completely dissolved, one equivalent of TFA was added and the reaction mixture was heated to 40 °C.

The employment of unsubstituted methyl ester **95a** resulted in only poor conversion of 11% when stirred at room temperature, the addition of TFA and heating improved the conversion to moderate 51% (entry 1). Moderate 35% conversion was achieved by mixing methylated methylester **96a** at room temperature in absence of TFA (entry 2). The respective ethylated ester **96b** achieved excellent 100% conversion by refluxing in presence of TFA (entry 3). The importance of warming the reaction mixture was proven by the reaction of disubstituted iodylarene **97a** firstly at room temperature resulting in only 2% conversion, which was improved to up to 51% conversion simply by heating (entry 4). On the other hand, iodyl derivative **90** achieved less than 1% conversion, even though the reaction mixture was refluxed at 82 °C overnight (entry 5). The influence of the addition of TFA in this reaction should be tested. Also, disubstituted nitrile **94a** gave improved conversions of 29% when heated, compared to the corresponding reaction at room temperature which only resulted in 3% conversion (entry 6).



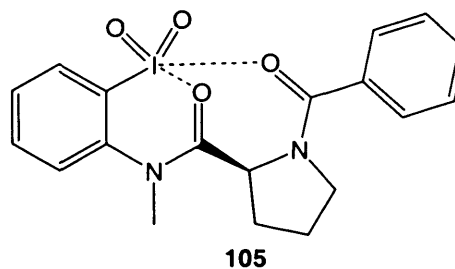
Entry	Iodol	Conversion ^a [%]	Conversion ^a [%] With TFA
1	 95a	11 (r.t.)	51 (reflux)
2	 96a	35 (r.t.)	
3	 96b		100 (40 °C)
4	 97a	2 (o/n, r.t.); 51 (o/n, reflux)	
5	 90	0.2 (reflux, o/n, acetonitrile)	
6	 94a	3 (r.t.), 29 (acetonitrile, reflux)	

^a determined by ¹H NMR analysis of the crude reaction mixture.

Table 4 Oxidation of benzyl alcohol with iodol compounds.

3.2.3.3 Oxidation of a Secondary Alcohol.

In the past, Zhdankin and co-workers synthesised iodyl derivatives **105** furnished with a (*S*)-proline moiety.^[61] These compounds were employed in the enantioselective oxidation reaction of *meso*-hydrobenzoin. In this way, only the (*S*)-hydroxy group was oxidised to the corresponding ketone in very promising enantioselectivities and good yields (41% ee, 79% yield) by stirring together with 0.5 equivalent of a iodyl derivative firstly at room temperature (1 h) and then at 65 °C in acetonitrile for three hours.



In the following reaction series, iodylarenes **94–98** were tested as suitable oxidants for the enantioselective oxidation of the secondary alcohol *meso*-hydrobenzoin. For this purpose, alcohol **106** was stirred together with iodylarenes in dichloromethane or acetonitrile at room temperature and heated conditions with or without the presence of TFA (Table 5). Only benzaldehyde **104** was recovered from the reaction conducted at room temperature and then heating to 65 °C using **95a** as oxidant without TFA; when TFA was added to the reaction mixture, only benzil **107** was found when the reaction was conducted at room temperature, whereas a mixture of **104** (32%) and **107** (68%) was detected, when the reaction mixture was heated to 40 °C (entry 1). A product mixture with similar ratios was observed, when methyl- and ethyl-substituted methylesters **96a** and **96b** were employed at 40 °C in presence of TFA (entries 2, 3). On the other hand, the employment of FIBX **102** as oxidant at room temperature and without the presence of TFA resulted in a product mixture of **104** (30%) and benzoin **108** (70%) (entry 4).^[59] Compound **108** was not detected in any other oxidation reaction.

In this reaction series, it becomes clear, that the temperature as well as the presence of TFA takes crucial influence on the products observed. Apart from the reaction employing FIBX **102** as oxidant, product mixtures of benzaldehyde **104** and benzil **107** were found, the latter being the major fraction, when the product mixtures were heated in presence of TFA. Only reactions either being heated or conducted in presence of TFA at room temperature resulted in either benzaldehyde **104** or benzil **107**. When FIBX **102** was employed at room temperature and without TFA, the major fraction of the reaction mixture was the originally desired product **108**. Further investigations of the reaction conditions should be done in order to eliminate the development of **104** in this reaction. These results suggest the oxidation strength of iodyl arenes synthesised in this project to be greater than the one of FIBX, since only compounds resulting from over-oxidation of *meso*-hydrobenzoin were observed.

Iodylarene **96a** was also employed in oxidation reactions of secondary alcohols such as cyclopentanol and 2,3-butanedione together with TFA in dichloromethane at 40 °C, but only starting material was recovered from these reactions.

Entry	Iodyl	Conversion ^a [%]	Conversion ^a [%] With TFA
1	 95a	100 % of 104 (MeCN, 65 °C)	32% of 104 , 68% of 107 (MeCN, 40 °C) 100% of 107 (MeCN, r.t.,)
2	 96a	-	32% of 104 , 68% of 107 (CH ₂ Cl ₂ , 40 °C)
3	 96b	-	35% of 104 , 65% of 107 (CH ₂ Cl ₂ , 40 °C)
4	 102	30% (20%) ^b of 104 , 70% (64%) ^b of 108 (MeCN, r.t.)	-

a determined by ¹H NMR analysis of the crude reaction mixture.
b isolated yield.

Table 5 Oxidation of *meso*-hydrobenzoin using iodylarenes with and without TFA.

3.2.4 Summary

Several commonly used oxidation methods have been applied to iodoarenes synthesised during this project and others; only two resulted in oxidised iodine compounds. Only λ^5 -iodanes could be synthesised and isolated, whereas possible products from reactions supposing to result in λ^3 -iodanes could not be isolated but probably decomposed during reaction work-up.

The iodylarenes synthesised were employed as oxidants together with different substrates, in order to determine their oxidative potential. Sulfides such as thioanisole, primary alcohols such as benzyl alcohol and secondary alcohols such as *meso*-hydrobenzoin were oxidised successfully to the respective sulfoxides, aldehydes and ketones. However, even though the iodylarenes employed in the oxidation of thioanisole were enantiomerically pure, the enantiomeric excess could be determined only for very few compounds for unexpected reasons, which could not be solved due to lack of time; further investigations could be done by others. A crystal structure was obtained and analysed.

3.3 Literature

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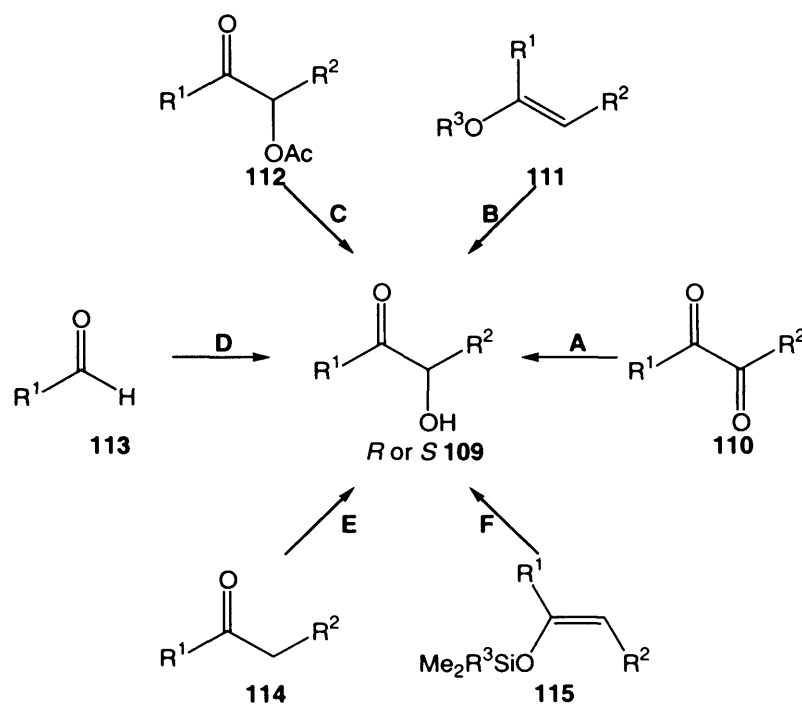
4.1 Catalytic Acetoxylation of Propiophenone

4.1.1 Introduction

4.1.1.1 Syntheses

α -Functionalised phenones are important intermediates in the synthesis of a variety of biologically active natural products and medicines. Since biological potency often depends on optical purity of the active molecule, enantioselective synthesis is of great concern. In the past, much work has been undertaken in order to develop efficient synthetic pathways towards α -hydroxy ketones **109**. Scheme 1 displays a selection of different starting materials for the preparation of compounds of the type of **109**. One possibility is the asymmetric reduction of diketones **110** using a chiral ruthenium catalyst (path **A**) leading to up to 99% enantiomerically pure products **109** in good yields.^[1] Another possibility for the enantioselective synthesis of α -hydroxy ketones **109** was developed by Sharpless and co-workers from enol ethers **111** and AD-mix- α or - β as oxidising reaction mixture (path **B**). These commercially available mixtures create a very potent osmium catalyst furnished with chiral ligands (e.g. (DHQD)₂PHAL) *in situ* and result in enantioselectivities up to 99%.^[2] In a third synthetic method already enantiomerically pure starting materials are used (path **C**). The acetate of the (*S*)-lactic acid derivative **112** was converted *via* a Friedel-Crafts reaction to the respective phenone followed by deprotection of the hydroxy group.^[3] Also, a enantioselective benzoin reaction catalysed by chiral triazolium-based perchlorates resulted in good selectivities up to 86% *ee* and acceptable yields of up to 72% (path **D**).^[4,5] Path **E** shows the introduction of different protective groups of the hydroxyl group in the α -position of ketones **114** such as triflates using thallium(III) triflates, which then can easily be converted into formate or acetate groups; however, the α -functionalised ketones **109** obtained are racemic and need to be resolved to be of any use for the synthesis of medicines.^[6] Another enantioselective method is the asymmetric oxidation of silyl enol ethers **115** using (salen)Mn(III) catalysts (path **F**). In this way, selectivities up to 87% are observed.^[7] Among many other

synthetic methods, enzymatic reduction of the corresponding α -diketone with baker's yeast or enzymatic kinetic resolution of the racemate of the protected or unprotected ketone **109** can be applied.^[8-11]

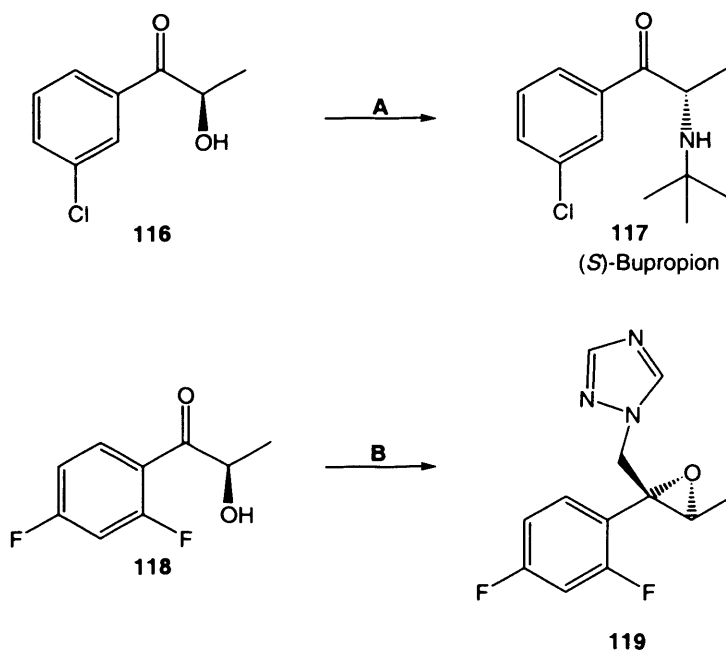


A: $R^1 = C_6H_5$, $R^2 = CH_3$, chiral Ru(II) catalyst, HCOOH (1.1 eq), $N(C_2H_5)_3$, 10–14 °C, up to 99% ee^[1] **B:** $R^1 = Cl$, $R^2 = CH_3$, $R^3 = CH_3$ or $Si(CH_3)_2^tBu$, AD-mix- α or $-\beta$ (1.8 eq), $^tBuOH/H_2O$ (1:1), $CH_3SO_2NH_2$ (1 eq), 0 °C, up to 99% ee^[2] **C:** $R^1 = Ar$, $R^2 = CH_3$, i) 45% H_2SO_4 , $pTsCl$ (53.7 mmol, 2 eq), pyridine (25 ml), –10 °C, 6h ii) concentrated $LiOH_{aq}$ solution, –15 °C, DMF, 5% NH_4Cl_{aq} ^[3,12] **D:** $R^1 = p\text{-MeC}_6H_4$, 30 mol% triazolium salt catalyst, Et_3N (33 mol%), MeOH, r.t., 83% ee^[5] **E:** $R^1 = C_6H_5$, $R^2 = CH_3$, $TiAc_3$ (1.5 eq), DMF (5 ml), CF_3SO_3H (4.5 eq), 60 °C, 96% yield^[6] **F:** $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = ^tBu$, NaOCl (7.5 eq), phosphate buffer (pH 11.3) or $PhIO$ (1.5 eq), PPNO (7 mol%), (salen)Mn complex (7 mol%), 86% ee.^[7]

Scheme 1 Synthetic pathways towards α -hydroxy ketones.

4.1.1.2 Application

Enantiomerically pure hydroxy ketones **109** are crucial starting materials for a variety of compounds used in pharmacy. Scheme 2 shows some examples of different compounds **109** and respective medicinal products. Ketone **116** is prepared from *m*-chlorophenyl propanone, which was converted into the respective silyl enol ether, followed by the Sharpless asymmetric dihydroxylation, conversion into an α -ketotriflate and amination using *t*-butylamine to give (*S*)-bupropion **117**, the active ingredient for an anti-depressive (Wellbutrin®, Glaxo Wellcome).^[13] Azole **119** (Sch42427/SM 9164) is an antifungal agent; the synthesis starts from the enantioselective hydroxylation of 2,4-difluoropropiophenone using camphorsulfonyl-oxaziridine to give **118**, followed by THP-protection of the hydroxy group and introduction of the triazole.^[14]

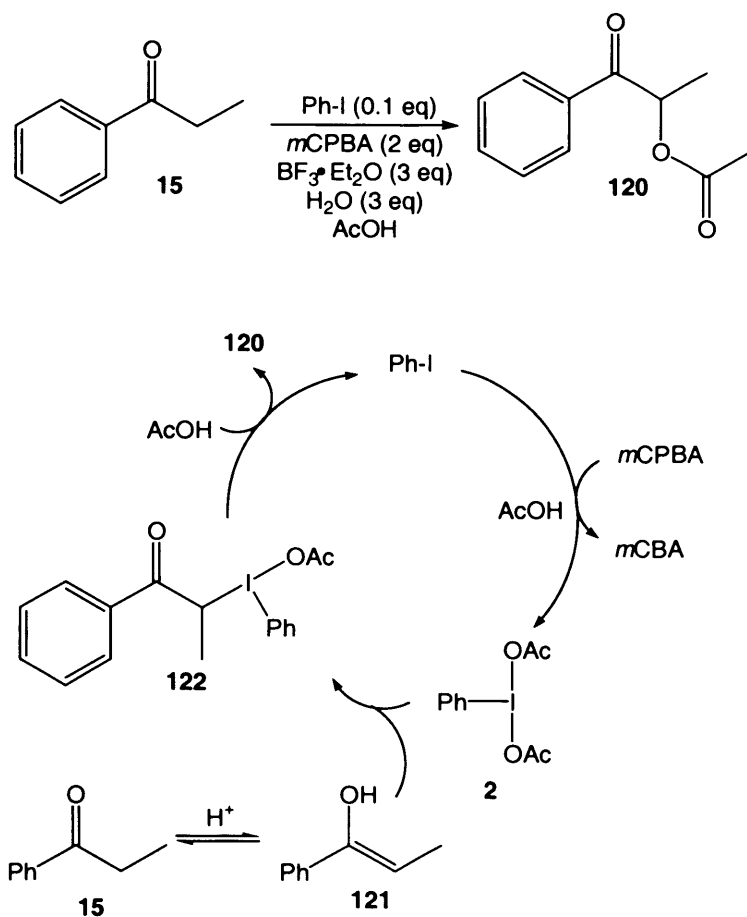


A: i) TiF_2O , Lutidine, CH_2Cl_2 , -40°C ii) $t\text{-BuNH}_2$, $-40 - 0^\circ\text{C}$, iii) $\text{HCl}/\text{Et}_2\text{O}$; **B:** i) (4 eq) DHP, PPTS ii) $\text{Me}_3\text{SOI}/\text{DMSO}/60\%\text{NaH}$, THF, 55°C iii) $\text{DMF}/\text{Na-Triazole}$, 70°C iv) HCl_{aq} or $p\text{TsOH}/\text{MeOH}$, H_2O v) $0-5^\circ\text{C}$, $t\text{PrOAc}$, Et_3N , MsCl , vi) $t\text{PrOAc}$, aq K_2CO_3 , r.t., $(\text{Bu})_4\text{NHSO}_4$.

Scheme 2 α -Hydroxylated phenones as starting materials for biological active compounds.

4.1.1.3 Acetoxylation of Propiophenone

The synthetic methods outlined above (Scheme 1), usually involve the use of toxic transition metals such as ruthenium (path **A**), osmium (path **B**) or thallium (path **E**). On the other hand, the use of hypervalent iodine compounds as non-toxic and environmental friendly reagents has been established in the past. Hypervalent iodine compounds have been employed in a variety of types of reactions (see Chapter 1). The first to use (diacetoxyiodo)benzene for the α -acetoxylation of ketones were Imamura and co-workers.^[15] Later, Ochiai and co-workers developed the catalytic use of iodine compounds (Scheme 3).^[16] In this reaction, inexpensive iodobenzene serves as catalyst, acetic acid as nucleophile and dried *m*CPBA as stoichiometric oxidant. Also, the presence of a Lewis acid such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is necessary in order to enlise the ketone; without a Lewis acid, iodobenzene was oxidised in presence of acetic acid, but acetoxylation of the phenone did not take place. Also, some water was added to the reaction mixture. In the absence of an iodine catalyst, no acetoxylation was observed, but the respective Baeyer-Villiger reaction product was obtained.



Scheme 3 α -Acetoxylation of propiophenone **15** catalysed by iodobenzene.

Iodobenzene is oxidised by *m*CPBA in presence of acetic acid to (diacetoxyiodo)benzene **2**. After addition of the double bond of the enolised phenone **121** to the partly positively charged iodine atom, thus forming intermediate **122**, acetic acid substitutes the iodine moiety in $\text{S}_{\text{N}}2$ -fashion, yielding product **120**.

4.1.1.4 Task

However, using iodobenzene as catalyst can only lead to racemic products. In order to achieve enantiomerically enriched α -acetoxyated phenones, a selection of chiral iodine compounds synthesised in this project (see Chapter 2) was employed.

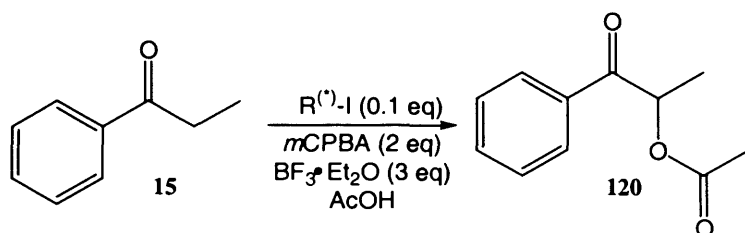
4.1.2 Results and Discussion

4.1.2.1 Enantioselective Acetoxylation of Propiophenone

A selection of enantiomerically pure iodine compounds synthesised in this project as well as commercially available non-aromatic compounds have been employed in the catalytic α -acetoxylation of ketones (Table 1). The stoichiometric oxidant *m*CPBA was not dried prior to the reaction, since some test reactions using iodobenzene as catalyst did not show any influence to the presence or absence of water. First, monosubstituted methyl ester **46b** was employed (entry 1). Even though an excellent conversion of 100% was achieved, only poor selectivity of 5% was observed. In order to investigate the influence of a more hindered moiety in the substituent, the benzyl-substituted catalyst **46c** was used (entry 2); again, very good conversions (99%) were achieved as well as the best (but still poor) enantioselectivity of 8%. Next, disubstituted ester **47b** was employed, resulting in very good conversions (99%), but poor selectivities (5%, entry 3). Then, an unsubstituted ester **45d** with a longer side chain in *ortho*-position to the iodine atom furnished with a bulkier and chiral ester moiety was used as catalyst (entry 4). Menthyl ester **45d** achieved excellent conversions, but very poor enantioselectivity of less than 5%. Also, the respective methyl substituted ester **46f** was employed in order to test the influence of a second asymmetric centre in *ortho*-position to the iodine atom (entries 5, 6). Methyl substituted menthyl ester (2*S*)-**46f** gave very good conversions of 100% (entry 5); enantioselectivity was second to the one achieved using **46c**, containing only one asymmetric centre (entries 5, 6% *ee*). Also, the respective (2*R*)-diastereomer was employed resulting in similar conversion (100%) and selectivity (4% *ee*). The respective menthyl ether iodoarene **73a** only resulted in 21% conversion and a racemic product (entry 7)¹. Only few λ^3 -iodanes containing a covalently bound non-aromatic alkyl moiety are known. Iodoacetonitrile **86** and methyl iodide **123**, for example, could not be isolated in their oxidised stage. In order to test, if they can be oxidised *in situ* to the respective (diacetoxyiodo)alkyls, they were employed as catalysts in the acetoxylation reaction (entries 8, 9).

¹ This reaction was performed by E. J. Holland, student project 2007

Both compounds resulted in excellent conversions of 99%, thus proving that they generally can be oxidised; only they are too unstable to be isolated. However, this is probably the first time, where alkyl iodides – which do not contain fluorine atoms – are successfully oxidised to their corresponding hypervalent stage. Now, also other chiral non-aromatic and non-fluorinated iodine compounds can be employed.



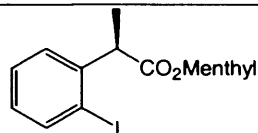
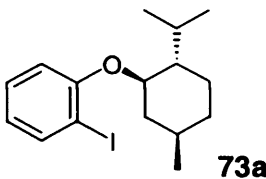

Entry	Catalyst	ee [%] ^a	Conversion [%] ^b
1	 (-)-46b	5	100
2	 (+)-46c	8	99
3	 (-)-47b	5	99
4	 45d	<5	99
5	 (2S)-46f	6	100

^a enantiomeric excess determined by HPLC

^b conversion determined from 1H NMR spectrum

Table 1 (continued on next page)

Enantiomerically pure iodoarenes and non-chiral alkyl iodides as catalysts.

Entry	Catalyst	ee [%] ^a	Conversion [%] ^b
6	 (2R)-46f	<5	100
7 ^c	 73a	0	21
8	 86	-	99
9	CH₃-I 123	-	99

a enantiomeric excess determined by HPLC

b conversion determined from ¹H NMR spectrum

c reaction done by E. J. Holland, student project summer 2007

Table 1 (continued) Enantiomerically pure iodoarenes and non-chiral alkyl iodides catalysts.

The poor enantioselectivity of this reaction has been experienced in the Wirth group before by others.^[17] The cause of this phenomenon is believed to be induced by strong intramolecular contacts between the iodine atom and the ester oxygen atom of the acetate groups (Figure 1).^[18] These interactions occupy the space at the iodine coordination sites thus inhibiting coordination of an oxygen atom from an *ortho*-side chain to the iodine atom. Without this interaction, the asymmetric side chain can rotate more freely, hindering interaction between the hypervalent iodine compound with the enolised phenone **121**.

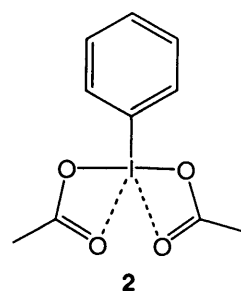


Figure 1

Summary. Enantiomerically pure α -acetoxyated ketones are important building blocks for many crucial intermediates of biological active compounds. Therefore, the development of non-toxic and environmental friendly as well as enantioselective catalysts is necessary. The use of chiral compounds gave quantitative conversions, but the enantioselectivities of all compounds employed were very poor and did not exceed 8%. On the other hand, alkyl iodides, which could not be oxidised so far, have been employed successfully; thus opening the possibilities to new types of iodocatalysts.

4.1.3 Literature

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4.2 Catalytic Halolactonisation of Pentenoic Acids

4.2.1 Introduction

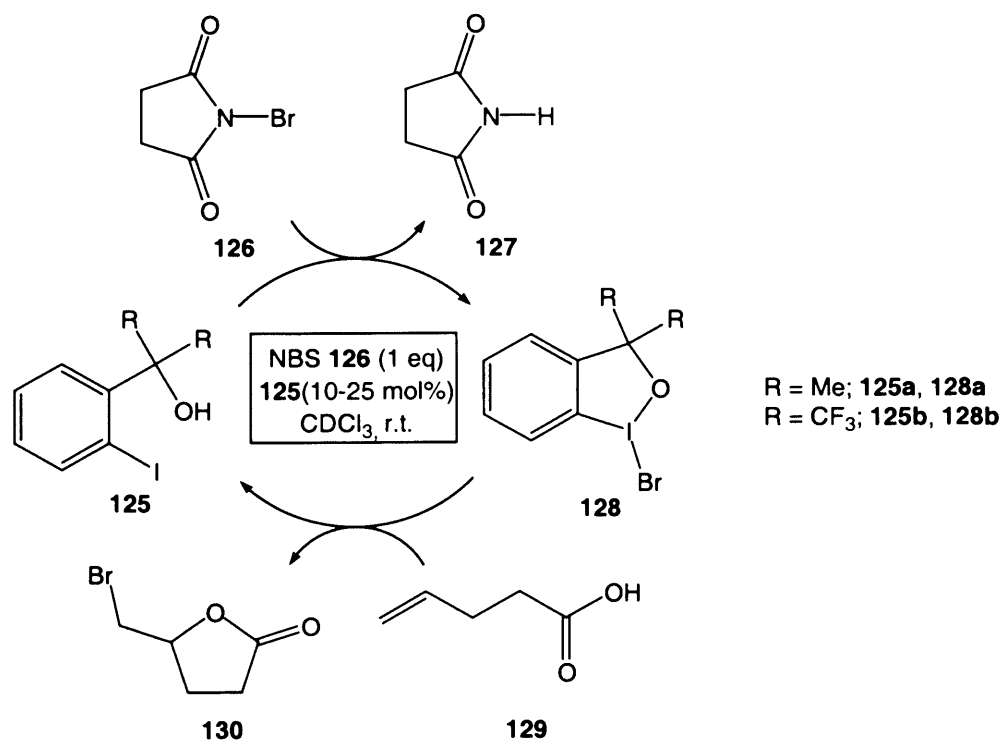
4.2.1.1 Early Halolactonisations

Halolactonisations have been of great interest since the end of the 19th century.^[1] Lactonisation is a widely used method in the synthesis of biologically active products such as prostaglandins.^[2] The halogen atom in halolactones can easily be substituted thus allowing a wide variety of possible synthetic strategies. In 1908 Bougault developed a synthetic method towards halolactones, namely iodolactones; the product was obtained by reaction of the respective unsaturated acid in aqueous sodium bicarbonate by addition of an iodine/potassium iodide solution.^[3,4] This work was extended by other groups, slightly varying reagents and conditions. This method has been used to distinguish α,β -unsaturated from respective β,γ -unsaturated acids, since the former will not result in iodolactones.^[5-8] It is believed that α,β -acids react extremely slowly under the conditions described.^[9] Also, bromo-^[10-16] and chlorolactonisations^[17-19] conducted with similar methods were established. Later, a method for iodolactonisation under neutral reaction conditions using thallium(I) carboxylate was described by Cambie.^[20] Further lactonisation methods include the use of hypobromites,^[21-25] cyanogen iodide,^[26] iodine azide^[27] and *N*-bromosuccinimide (NBS).^[28] The halolactonisation method using mercury oxide proceeds through the formation of radicals.^[29-32] Also, enantioselective cyclisation reactions have been investigated, using e.g. chiral iodine complexes of dihydroquinidine or asymmetric pyridines or amines.^[33-37]

Several approaches towards bromination reactions using hypervalent iodine compounds, mainly readily available DIB, have been undertaken. Some examples of these reactions are bromination of flavones^[38,39] or dihydropyrans^[40] employing TMSBr or Bu₄NBr together with DIB or bromoacetoxylation of 1,4-methoxynaphthalenes using TMSBr and DIB.^[41] Braddock and co-workers developed a synthetic method for bromination and lactonisation of activated aromatics and olefins or unsaturated acids, respectively, since at present the widely used reagent for electrophilic bromination is molecular bromine, which is a toxic and lachrymatory liquid.^[42] It was expected that in reactions employing benevolent non-toxic hypervalent iodine compounds, the respective starting material could be stirred together with a slight excess of lithium bromide in dry THF and stoichiometric amounts of DIB **2**, which would undergo a ligand exchange with lithium bromide to gain a λ^3 -iodane

Scheme 1 *In situ* preparation of (acetoxybromiodo)benzene **124** as a new bromination reagent.

Indeed, brominated activated aromatics, heteroaromatics, lactones and the dibromination of olefins were achieved after short reaction times of 30 minutes in moderate to good yields. It was found, that *ortho*-substituted iodanes of type **128** can alternatively be synthesised in moderate yields by treatment of the respective iodoarenes **125** with NBS **126**.^[43] The above facts prompted the development of the catalytic bromolactonisation of unsaturated acids (Scheme 2).^[44] Different unsaturated acids such as **129** were stirred together with NBS and 10–25 mol% iodoaryl catalyst for 0.25–24 h (depending on the catalyst) in chloroform at room temperature, to give the respective lactones in excellent conversions of 100%. The reaction progress was very slow (15 h, 20% conversion), when the reaction was performed without catalyst.

Scheme 2 Iodoarene-catalysed bromolactonisation of 4-pentenoic acid **129**.

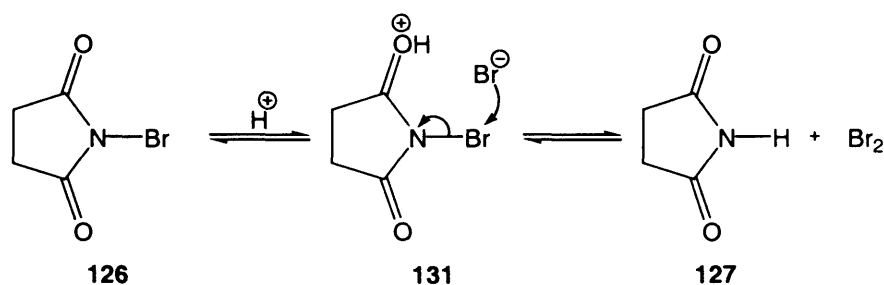
4.2.1.2 Task

However, no catalytic halolactonisation using enantiomerically pure iodoarenes have been reported so far. In the following, the results of halolactonisation reactions employing different iodoarenes prepared during this project will be presented. As sources of halogen, NBS as well as *n*Bu₄NBr were used in different reactions.

4.2.2 Results and Discussion

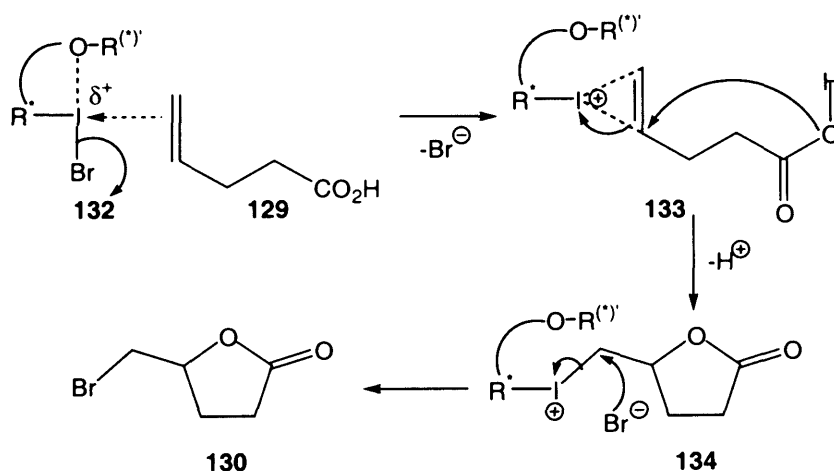
4.2.2.1 Reaction Mechanism

The choice of solvents plays a crucial part as a closer look at the mechanism of reactions using NBS demonstrates (Scheme 3). In protic solvents, an equilibrium of NBS **126** and protonated NBS **131** is formed; **131** can be attacked by a bromide, thus providing a good source of Br_2 in low concentrations in reactions; indirectly, a convenient source of “ Br^+ ” is provided. Bearing this mechanism in mind, no protic solvents should be used as solvents for the iodoarene catalysed bromolactonisation of pentenoic acids.



Scheme 3 NBS as source of Br_2 in low concentration.

The mechanism of the iodoarene catalysed reactions is believed to proceed as displayed in Scheme 4. Similarly to the reaction mechanism in Scheme 3, the iodoarene can attack NBS **126** to form a (bromoiodo)arene species **132**. After formation of an iodonium complex **133** *via* a π -complex, an oxygen atom from the carboxylic acid moiety of **133** can attack, thus forming the iodolactone **134**. In the final step, the Br^- substitutes the iodine moiety in $\text{S}_{\text{N}}2$ -fashion to give the final product **130**.^[42]



Scheme 4 Possible mechanism of iodoarene catalysed bromolactonisation of 4-pentenoic acid **129**.

An alternative mechanism could be the direct electrophilic bromine transfer under loss of acetate and generation of iodobenzene. In order to determine the reaction mechanism, 4-pentenoic acid was treated once with molecular bromine as well as with bromine acetate (AcOBr), which also could be formed in this reaction. In case of the use of molecular bromine, a considerable amount of dibromination at the double bond was observed (50%). When authentically synthesised bromoacetate^[45] was employed as source of a Br⁺ ion only 50% conversion to the lactone was detected alongside 25% formation of dibrominated acid.^[42]

4.2.2.2 Finding Suitable Solvents

Firstly, bromolactonisation reactions with the different pentenoic acids were done using NBS only, without catalyst. The lactonisation of 4-pentenoic acid **129** proceeded to completion within less than one minute, when NBS was not recrystallised and was slightly yellow from traces of elemental bromine, which can complete the reaction. The reaction time was remarkably longer, when freshly recrystallised, white NBS^[46] was used², so that a chiral catalyst could take influence on reaction rate and enantioselectivity.

In order to ensure that product development from background reactions by liberated bromine was not interfering, a reaction series only employing NBS was carried out. Several aprotic solvents were tested in order to determine the most suitable one (Scheme 5, 6). For this purpose, 4-pentenoic acid **129** was added to an NMR tube together with one equivalent of freshly recrystallised NBS in a deuterated solvent and NMR (250 MHz) measurements were done repeatedly in order to determine the reaction progress. For comparison of the reaction progress in presence of a catalyst, the reaction was done using iodoarene **46b** (10 mol%) together with one equivalent of recrystallised NBS in deuterated chloroform and an acid **129**. Schemes 5 and 6 display the results of the measurements for 4-pentenoic acid **129** and 2-cyclopentene-1-acetic acid **135**; a suitable linear fit was calculated using Windows Excel, thus giving the matching formula to reaction progress of linear type,

$$y = \mathbf{a}x + \mathbf{b},$$

y = linear function of the respective reaction
 \mathbf{a} = gradient
 \mathbf{b} = y-intercept

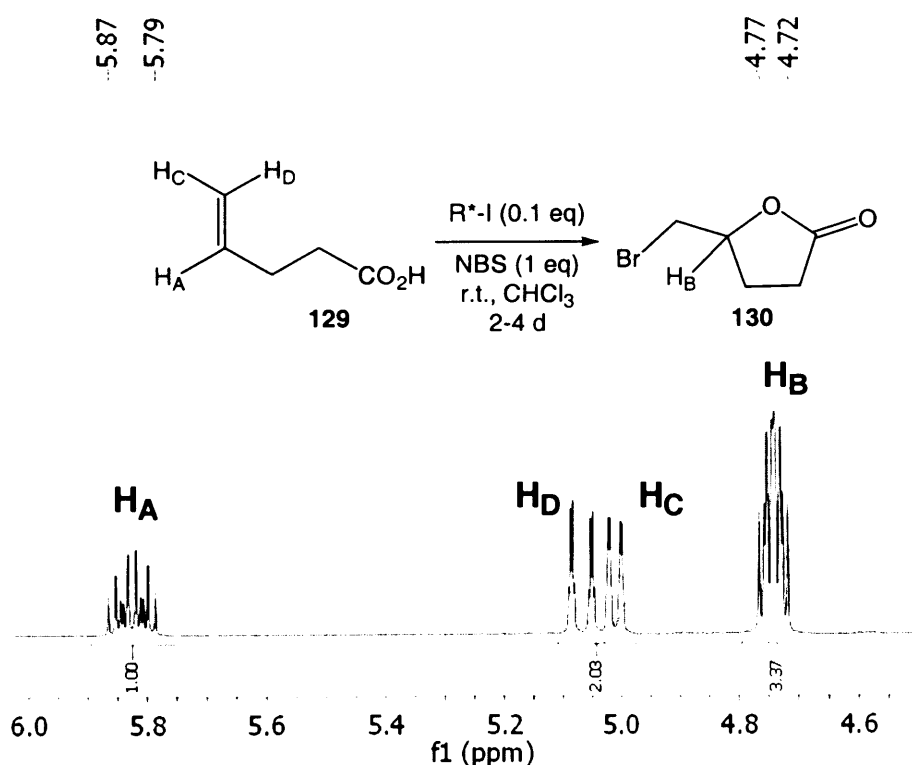
whereupon **b** is not of interest here and can be neglected, whereas **a** is the value representing the wanted information. It is understood, that these measurements as well as their linear

¹ prepared *in situ*; activity confirmed by conversion of *cis*-cyclooctene to *trans*-1-bromo-2-acetoxy-cyclooctane.

² NBS was recrystallised from boiling distilled water by B. Ojo.

interpretation do not represent realistic conditions; however, only very crude and quick investigations could be done for time reasons. Also, it is realised, that a more detailed investigation of these graphs would not lead to a linear representation, if more data points were obtained. Usually, for kinetic investigations of this kind the determination of the reaction order by measurement of the concentration of the different reagents depending on time would be done. A graph compiled by the data observed, would give information about the reaction order: for first order, the graph obtained by logarithm of the concentration vs time would be linear. For second or third order, a linear graph is obtained from the reciprocal of the concentration vs time or the reciprocal of the square of the concentration vs time. In the present case, more accurate measurements should have been done in order to determine the reaction rate.

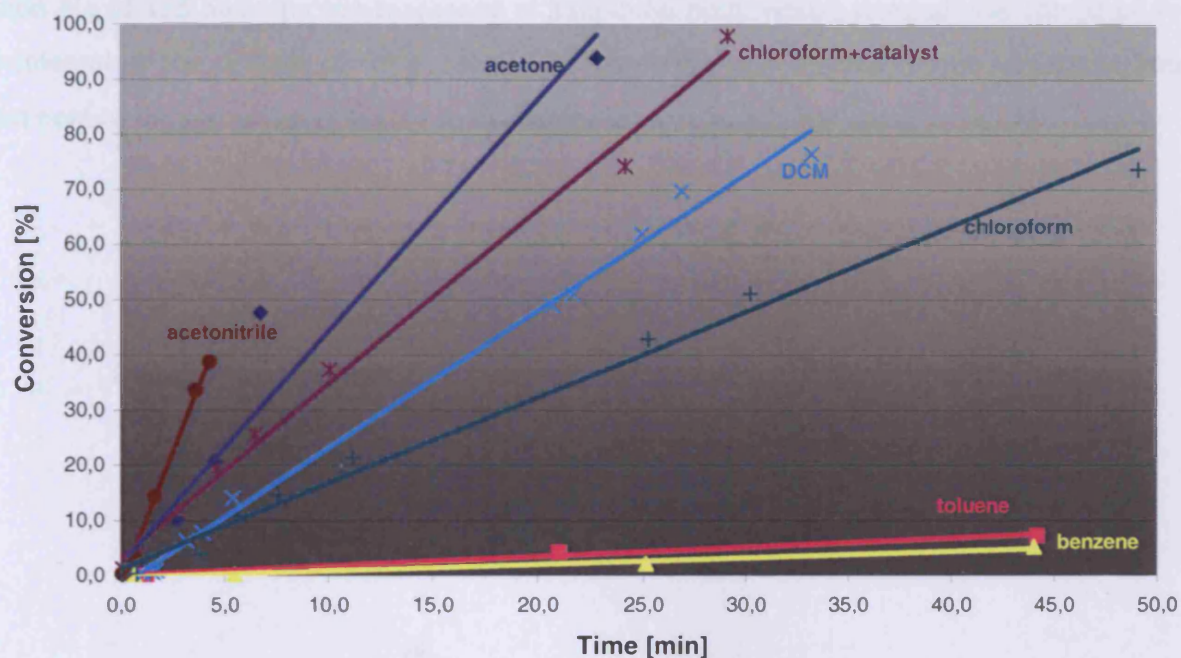
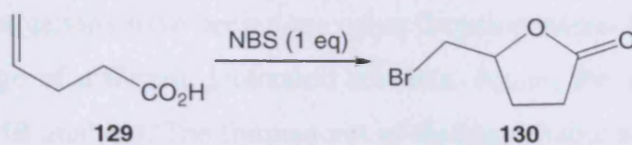
Conversions were determined from ^1H NMR spectra. Starting material and product peaks can clearly be distinguished as shown in Scheme 5. The multiplett of vinylic proton H_A possesses a proton frequency at 5.79–5.87 ppm, whereas the proton H_B attached to the tertiary carbon atom in product **130** exhibits a proton frequency at 4.72–4.77 ppm. The comparison of the integrals of these peaks gives the reaction conversion.



Scheme 5 Cut-out of a ^1H NMR spectrum displaying the reaction progress of the bromolactonisation of 4-pentenoic acid **129**.

However, the reaction rates obtained this way can not represent the actual reaction rate of these reactions, since the reaction mixtures are not stirred as they would be in a flask. On the other hand, all reactions compared were conducted under similar conditions and can at least provide a rough representation.

The first reaction series was done using 4-pentenoic acid **129** as starting material (Table 1). Only deuterated solvents were used for these reactions. The solvent achieving the highest reaction rate when only NBS was added to **129** was acetonitrile with 9.5 %/min and therefore was unsuitable for this reaction. About half of this rate was achieved by the respective reaction in acetone with 4.2 %/min, followed by the rate observed, when dichloromethane (CH_2Cl_2) was used as solvent (2.5 %/min). The use of chloroform as solvent resulted in acceptable 1.6 %/min; slowest reaction rates were observed when aromatic solvents toluene and benzene were employed (0.2 and 0.1 %/min). However, the use of benzene together with an iodine catalyst was tested with cyclopentenoic acid and resulted in very slow conversion. The catalysed reaction resulted in enhanced reaction progress of 3.2 %/min in chloroform, which seemed to be suitable for this reaction series (entry 7).

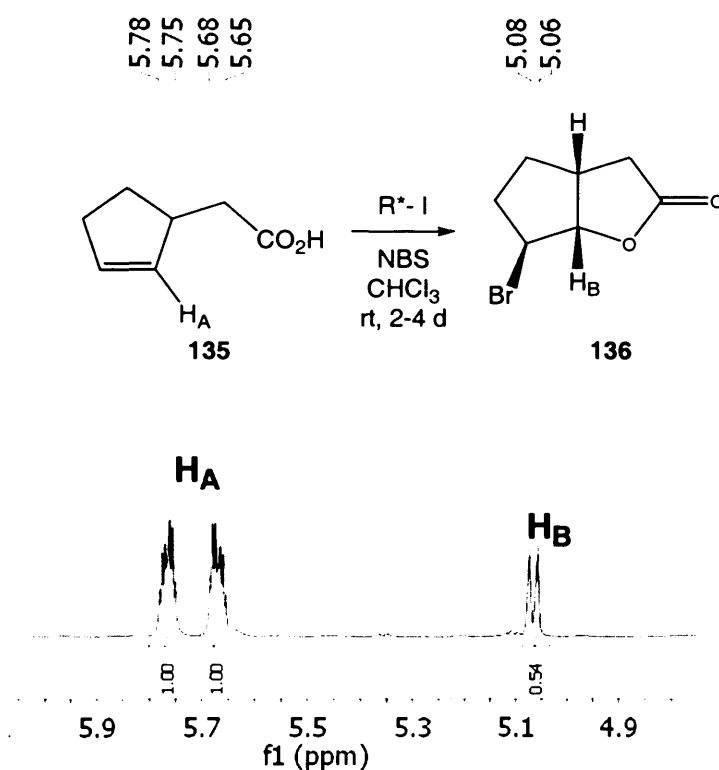


Entry	Solvent	Gradient a [%/min]
1	CH ₃ CN	9.5
2	(CH ₃) ₂ CO	4.2
3	CH ₂ Cl ₂	2.5
4	CHCl ₃	1.6
5	C ₆ H ₅ CH ₃	0.2
6	C ₆ H ₆	0.1
7 ^a	CHCl ₃	3.2

a a catalyst was added to this reaction (entry 7).

Table 1 Bromolactonisation of 4-pentenoic acid **129** using recrystallised NBS in different solvents.

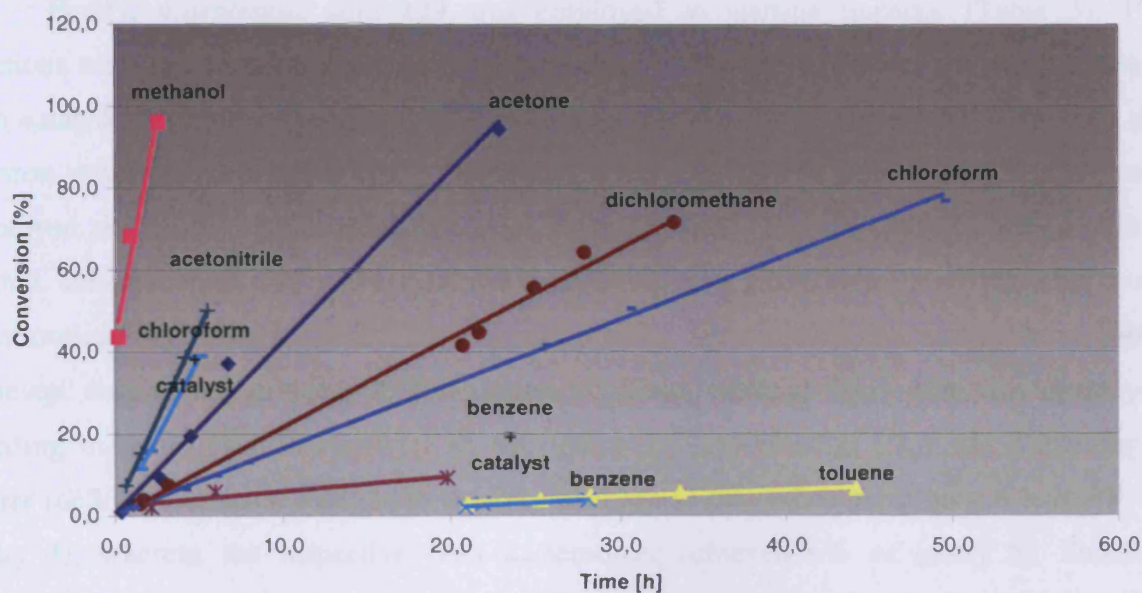
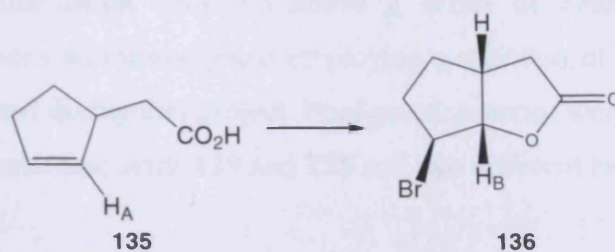
Also, similar investigations have been done using 2-cyclopentene-1-acetic acid **135** as starting material in a range of different deuterated solvents. Again, the reaction conversion was determined by ^1H NMR analysis. The frequencies of distinguishable starting material and product protons were selected for integral comparison (Scheme 6). The multiplet of a vinylic proton H_A of **135** has a proton frequency at 5.65–5.68 ppm, whose integral was compared to the integral of the doublet of the proton H_B (5.06–5.08 ppm) attached to the tertiary carbon atom next to the carbon atom linked to the bromide atom in product compound **136**.



Scheme 6 Determination of the reaction conversion of the bromolactonisation of 2-cyclopentene-1-acetic acid **135** by ^1H NMR analysis (cut-out of a respective spectrum).

Although it is known, that protic solvents should not be used for this reaction, one reaction was conducted in methanol, in order to determine the faster reaction rate, out of curiosity (Table 2). The by far highest reaction rate of 21.25 %/min was observed, when methanol was used as solvent (entry 1), which therefore is truly unsuitable for this reaction series. The second highest rate of 8.71 %/min was achieved by the use of acetonitrile as solvent (entry 2). About half of this rate was obtained by the employment of acetone (entry 3). When dichloromethane was used, 2.18 %/min of reaction rate was observed (entry 4),

followed by a rate of 1.57 %/min, when chloroform was used (entry 5). The lowest (and therefore most desirable) reaction rates were achieved, when aromatic solvents such as benzene (entry 6) and toluene (entry 7) were used, resulting in 0.21 and 0.15 %/min, respectively. The rate of a reaction using deuterated benzene as solvent and employing catalyst **45d** (10 mol%) alongside acid **135** and NBS (1 eq) was determined. The rate observed was not essentially higher than the rate of the background reaction (entry 8, 0.4 %/min). Therefore, another catalysed reaction using **45d** was done in deuterated chloroform (entry 9), which resulted in the second slowest reaction rate. In this reaction, a rate of 7.6 %/min was observed and proved chloroform to be the most efficient solvent for the catalytic bromolactonisation of pentenoic acids, since the difference of the rates of reactions with and without the employment of an iodoarene catalyst is high, which shows the catalyst taking a crucial influence in this reaction.



Entry	Solvent	Gradient a [%/min]
1	CH ₃ OH	21.25
2	CH ₃ CN	8.71
3	(CH ₃) ₂ CO	4.18
4	CH ₂ Cl ₂	2.18
5	CHCl ₃	1.57
6	C ₆ H ₆	0.21
7	C ₆ H ₅ CH ₃	0.15
8 ^a	C ₆ H ₆	0.4
9 ^a	CHCl ₃	7.6

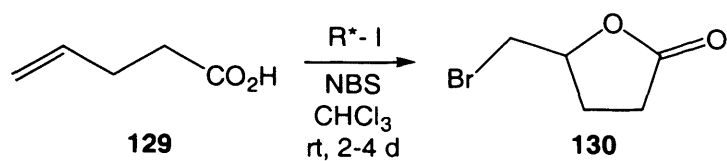
a catalyst (10 mol%) was added to this reaction (entries 8, 9).

Table 2 Bromolactonisation of 4-pentenoic acid **135** using recrystallised NBS in different solvents.

Based on the information collected above a series of enantioselective catalytic bromolactonisation reactions was investigated employing a selection of new enantiomerically pure iodoarenes synthesised during this project. Four reaction series were investigated, testing commercially available pentenoic acids **129** and **135** and two different bromination reagents.

4.2.2.3 Bromolactonisation of 4-Pentenoic Acid using NBS

Firstly, 4-pentenoic acid **129** was employed as starting material (Table 3). The reactions were conducted using freshly recrystallised NBS as stoichiometric oxidant together with catalytic amounts of an enantiomerically pure iodoarene and chloroform as solvent; the reaction mixtures were left to stir at room temperature for two to four days. All iodoarenes employed as catalysts gave excellent conversions of 100%. Ester (–)-**46a** furnished with a methyl substituent in the *ortho*-side chain resulted in good conversions, but only poor enantioselectivity of 4% (entry 1). The respective ethyl-substituted iodoarene (–)-**46b** achieved similar selectivities of 3% (entry 2). Short menthyl ester **60b** was employed resulting in better enantioselectivity of 6% (entry 3). (2*S*)-Menthyl ester **46f** containing a longer methyl-substituted side chain in *ortho*-position to the iodine atom gained only 3% *ee* (entry 4), whereas the respective (2*R*)-diastereomer achieved 6% *ee* (entry 5). Enantiomerically pure methyl substituted nitrile (–)-**39a** resulted in 4% *ee* (entry 6); nitrile (–)-**40c** furnished with an additional benzyl substituent only gained 2% *ee* (entry 7). The absolute configuration of **130** was not determined since the enantiomeric excess of the reaction was quite poor.



Entry	R*-I	ee [%] ^a	enriched Fraction ^b	Conversion [%] ^c
1	 (-)-46a	4	2	100
2	 (-)-46b	3	1	100
3	 60b	6	2	100
4	 (2S)-46f	3	2	100
5	 (2R)-46f	6	2	100
6	 (-)-39a	4	2	100
7	 (-)-40c	2	1	100

a determined by GC.

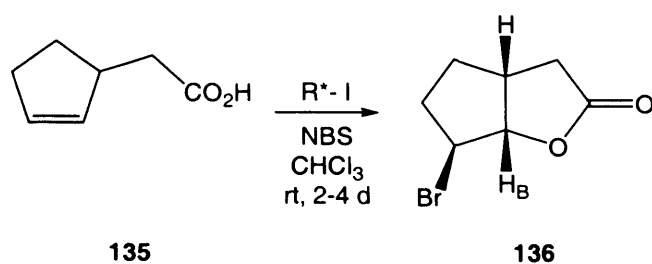
b enriched fraction observed from GC.

c determined by ¹H NMR.

Table 3 Enantioselective catalytic bromolactonisation of 4-pentenoic acid **129**.

4.2.2.4 Bromolactonisation of 2-Cyclopentene-1-acetic Acid using NBS

Another acid suitable for the catalytic bromolactonisation is 2-cyclopentene-1-acetic acid **135**. Good conversions were achieved when methyl substituted ester (–)-**46a** was employed as catalyst, but only poor enantioselectivity of 4% was found (Table 4, entry 1). Then, short menthyl ester **60b** was employed, resulting in only moderate conversion of 44% and poor enantioselectivity (5%, entry 2). Menthyl ester **45d** containing a longer side chain in *ortho*-position to the iodine atom gained very high conversion (99%), but only 3% *ee* (entry 3). Ester **46f** furnished with an additional methyl substituent in the side chain was the most potent catalyst in other reactions; the bromolactonisation reaction catalysed by **46f** achieved excellent conversions for both diastereomers, but only very poor selectivities of 1 and 3% (entries 4,5). One explanation for the different reactivities of iodoarenes furnished with longer side chains compared to shorter ester **60** could be, that the iodine atom is blocked by the bulky menthyl moiety. The longer side chain in ester **45** moves the bulky moiety further away from the iodine atom. On the other hand, this also causes decreased selectivities. Also, enantiomerically pure nitriles were employed as catalysts: nitrile (–)-**39a** with one methyl substituent in the side chain gained excellent conversions of 94%, enantioselectivity observed were poor (4%) (entry 6). The highest enantioselectivity of 5% *ee* in this reaction series was achieved alongside excellent conversions of 99%, when disubstituted nitrile (–)-**40c** was employed (entry 7). Compound **45e** failed to achieve any enantioselectivity this reaction (entry 8). In addition, methyl iodide **123** was used as catalyst, which so far could not be isolated in the oxidised λ^3 -state (entry 9), resulting in very good conversion of 100%, thus proving once more the new possibilities of catalytic reactions towards employment a far greater range of iodine compounds for *in situ* creation of hypervalent compounds.



Entry	R*-I	ee [%] ^a	enantioenriched Fraction	Conversion [%] ^b
1	 (-)-46a	4	1	84
2	 60b	5	2	44
3	 45d	3	2	99
4	 (2S)-46f	1	2	99
5	 (2R)-46f	3	2	98
6	 (-)-39a	4	1	94
7	 (-)-40c	5	1	99
8	 45e	0	-	98
9	MeI 123	-	-	43

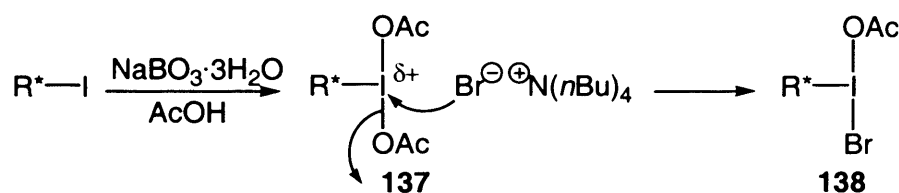
^a determined by HPLC.

^b determined by ¹H NMR.

Table 4 Enantioselective bromolactonisation of 2-cyclopentene-1-acetic acid **135**.

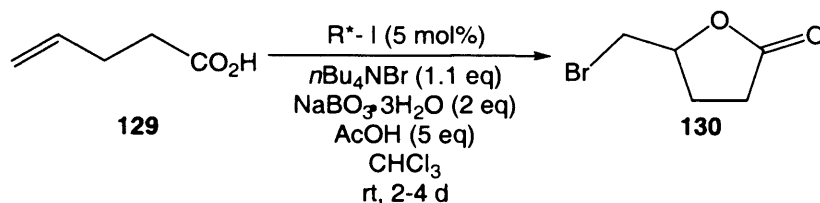
4.2.2.5 Bromolactonisation of 4-Pentenoic Acid using $n\text{Bu}_4\text{NBr}$

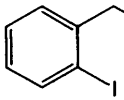
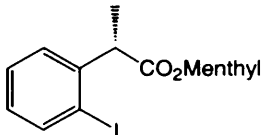
In the reaction series using $n\text{Bu}_4\text{NBr}$ as bromide source, the iodoarene (5 mol%) was firstly oxidised to the corresponding diacetoxy derivative **137** *in situ* (Scheme 7). For this purpose, these catalytic reactions were conducted using excess $\text{NaBO}_3 \cdot 3\text{H}_2\text{O}$ and acetic acid. Then, one acetoxy-moiety of **137** can be replaced by a bromide anion provided by $n\text{Bu}_4\text{NBr}$. Once the emerging (acetoxymoiiodo)aryl species **138** is formed, the mechanism might proceed as shown in Scheme 4 for reactions using NBS as halogen source.



Scheme 7 Possible formation of (acetoxymoiiodo)arenes **138**.

Three iodoarenes have been tested as catalysts (Table 5). Iodobenzene was employed in order to test if the desired product **130** could be synthesised with this method, resulting in good 94% conversion (entry 1). As enantiomerically enriched catalysts, menthyl ester **45d** (entry 2) and the respective methyl-substituted ester (2*S*)-**46f** (entry 3) were employed, both achieving excellent conversions of 100%, but only enantioselectivity of 5% and 3%, respectively. Surprisingly, catalyst (2*S*)-**46f** containing a chiral centre closer to the iodine atom resulted in lower selectivity than **45d**; on the other hand, the difference between these two results is not very high, thus not really allowing any conclusion to be drawn.



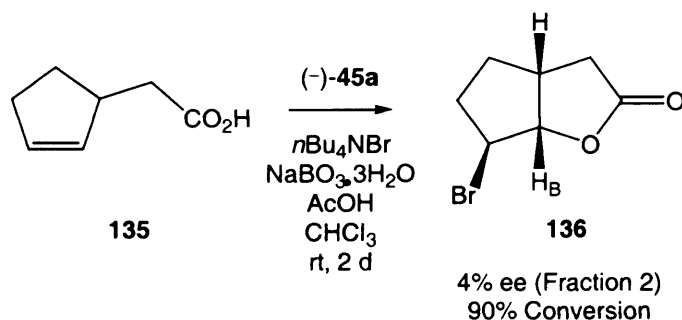
Entry	R*-I	ee [%] ^a	enriched Fraction	Conversion [%] ^b
1	Ph-I	-	-	94
2	 45d	5	1	100
3	 (2S)-46f	3	2	100

a determined by HPLC.
 b determined by ¹H NMR.

Table 5 Catalytic bromolactonisation of **129** using *n*Bu₄NBr as source of a bromide anion.

4.2.2.6 Bromolactonisation of 2-Cyclopentene-1-acetic Acid using *n*Bu₄NBr

The reactions were conducted as described above; for time reasons only ester (–)-**46a** could be tested (Scheme 8). Methyl ester (–)-**46a** furnished with a methyl substituent in the side chain resulted in good conversion of 90% and in 4% enantioselectivity. The reaction conversion was determined by ¹H NMR and the enantiomeric excess by HPLC using a chiral stationary phase (see Chapter 5).



Scheme 8 Lactonisation of acid **135** using *n*Bu₄NBr as source of a bromide anion.

4.2.2.7 Conclusions and Summary

Two catalytic reaction methods for the bromolactonisation of pentenoic acids were tested employing enantiomerically pure iodoarenes synthesised during this project; firstly NBS was used as source of bromine, followed by the use of *n*Bu₄NBr together with oxidising reagents in order to generate hypervalent compounds *in situ*. Usually excellent conversions were achieved, the enantiomeric excess on the other hand remained disappointingly low for all methods and catalysts.

No enantioselective trend could be observed in all reactions and methods; the stereochemistry of the catalysts seems to make very little difference: when pentenoic acid was used as starting material together with NBS (Table 1), catalyst (–)-**46a** resulted in slightly enantioenriched product **130**, the second fraction being the major enantiomer (entry 1), whereas catalyst (–)-**46b** of similar configuration as (–)-**46a** resulted in **130** with the first fraction dominating (entry 2). Both diastereomers of menthyl ester **46f** were employed resulting both in the same enantioenriched product (entries 4,5). The fact that menthyl ester **60b** not furnished with a second asymmetric centre resulted in the similar configured product in slightly higher enantioselectivity, leads to the thought, that the additional asymmetric centre does not make any difference in the enantioselection of this reaction.

The same phenomenon was observed, when 2-cyclopentene-1-acetic acid was used as starting material (Table 2): menthyl esters **45d** and **60b** without additional chiral centre resulted in enantioenriched products; the second fraction is the dominant one. This result does not change for both diastereomers of menthyl ester **46f**; again, the asymmetric centre closer to the iodine atom does not seem to confer any influence. Nitriles **39a** and **40c** result in products with a dominant first enantioenriched fraction. In order to find out more about the influence about a asymmetric centre in *ortho*-position to the iodine atom without the presence of a chiral ester moiety, also the respective (+)-enantiomer of **46a** should be employed as catalyst.

Only few catalysts could be tested in reactions using *n*Bu₄NBr as bromine source. For **123** as starting material only up to 5% *ee* were observed, when catalyst **45d** was employed (Table 5, entry 2), which is not furnished with an additional asymmetric centre closer to the iodine atom. Nevertheless, the additional chiral centre seems to exert crucial influence in this reaction, since the opposite configured product was recovered when (2*S*)-**46f** was used as catalyst (entry 3). Only one catalyst was tested for **135** as starting material, achieving only 4% enantioselectivity (Scheme 8). Now, also (2*R*)-**46f** should be employed as catalyst in order to investigate, if products **136** achieved have opposite or similar configurations.

The nature of the hypervalent iodine compound generated *in situ* cannot be determined at present for now. One possibility is the formation of compound **124** from a DIB derivative as stated by Braddock and co-workers. On the other hand, it is also possible, that the iodonium complex is formed by the DIB derivative and the bromide ion emerges directly from the halogen reagent. The first possibility comprehends the formation of a λ^3 -iodane containing a rigid asymmetric moiety *via* the oxygen bridge linked to the iodine atom is formed possibly as shown in Scheme 2, which could lead to increased enantioselectivity. This argument is weakened by the fact, that DIB-derived λ^3 -iodane (2*S*)-**46f**, where the asymmetric moiety can rotate freely, achieved enantioselectivities of 3% (Scheme 10, entry 3), whereas the same catalyst gave the exact same result, when NBS was used (Scheme 7, entry 4).

In summary, no trend towards any formation of enantioselectivity depending on the structure of catalysts could be observed. In order to achieve improved enantioselectivities, iodine compounds with different structures should be employed as catalysts; especially non-aromatic chiral iodine compounds could be tested, since they have shown catalytic activity in other reactions and definitely would broaden the variety of iodocatalysis.

4.2.3 Literature

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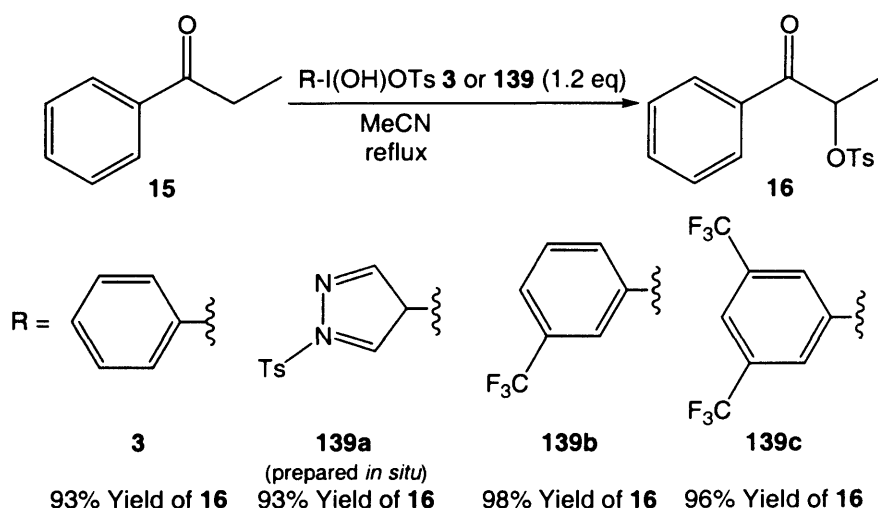
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4.3 Catalytic α -Oxysulfonylation of Phenones

4.3.1 Introduction

Functional groups next to carbonyl groups carry great potential in organic synthesis. The chemistry of e.g. α -halo ketones is studied in great detail,^[1] whereas α -sulfonyl ketones containing the same general features in the sense of containing a good leaving group attached next to a carbonyl group, has not been investigated thoroughly.^[2] α -Sulfonyl ketones contain not only a better leaving group than the α -halo ketones but the sulfonyl group is a strong electron-withdrawing group and acidifies the α -hydrogen notably.^[3] However, a range of applications has been established such as ring contractions in cyclic α -tosyloxyketones as Favorskii-type reactions,^[4] synthesis of heterocycles^[5] or as thiol-specific electrophiles^[6] to name a few. Also, α -sulfonylketones can form synthetically useful intermediates for e.g. tumour-localising compounds^[7] or anti-inflammatory drugs.^[8]

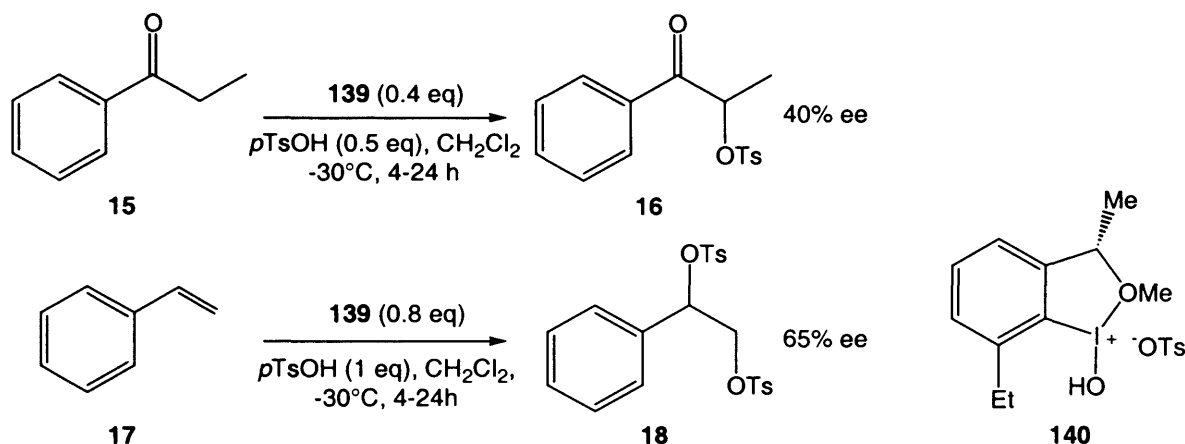
Synthetic routes towards α -sulfonylketones include a one-pot synthesis from alkenes together with DMDO, *p*TsOH and DMP,^[5] the reaction of enol acetates with arylsulfonyl peroxides in methanol,^[9] or the use of thallium(III)-*p*-tolylsulphonate and enolisable ketones.^[10] Koser and co-workers developed a synthetic route towards α -tosyloxy ketones **16** by refluxing a ketone together with [hydroxy(tosyloxy)iodo]benzene **3** ("Koser's Reagent") in acetonitrile or in dichloromethane at room temperature for reactions with cyclohexanone (Scheme 1).^[11] Togo and co-workers extended the range of [hydroxy(tosyloxy)iodo]arenes to compounds bearing e.g. thienyl, *N*-tosyl-4-pyrazolyl **139a** or 3-trifluoro- methylphenyl **139b**



Scheme 1 α -Tosyloxylation of ketones reactions using derivatives of Koser's reagent.^[12]

as aromatic moiety and employed these in α -tosyloxylations reactions of ketones by refluxing in acetonitrile for 0.5 to 18 hours.^[12]

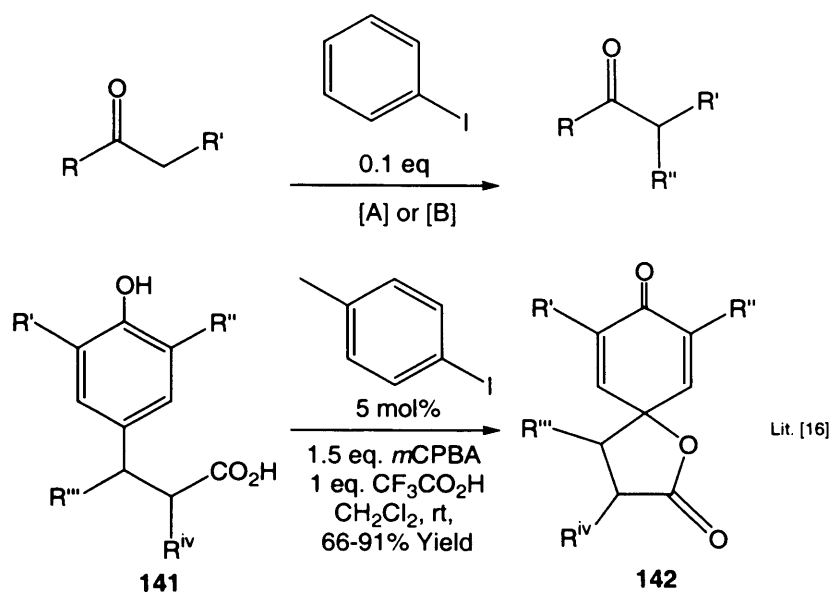
In 2001 Wirth and co-workers employed asymmetric iodanes such as **140** in the enantioselective oxytosylation of propiophenone and dioxytosylation of styrene (Scheme 2).^[13] Reactions usually were conducted in dichloromethane at $-30\text{ }^{\circ}\text{C}$ in order to improve enantioselectivities and achieved moderate enantioselectivities of up to 40% *ee* for α -oxytosylations and 65% *ee* for dioxytosylations.



Scheme 2 Stoichiometric functionalisation reactions using asymmetric iodanes.

In these reactions, the Koser reagent-type iodane **140** has to be used in stoichiometric amounts. On the other hand, a range of enantiomerically pure iodine compounds has been synthesised but remained untested, because oxidation to the respective aryl λ^3 -iodanes or the isolation of the respective iodanes due to poor stability has been unsuccessful so far.

Recently, the catalytic use of iodine compounds has been developed. Catalytic reactions such as anodic *gem*-difluorination of thiodiketals,^[14] α -acetoxylation of phenones (Scheme 3)^[15] and spirolactonisation of hydroxyphenyl propionic acid **141**^[16] (Scheme 3) were developed. Shortly after, Togo and co-workers used similar reaction conditions for the α -oxytosylation of phenones in good yields.^[17] In addition to iodoarene as catalyst, *m*CPBA, well known as a potent oxidation reagent in the synthesis of λ^5 -iodanes, was used as stoichiometric oxidant and *p*TsOH as nucleophile (Scheme 3).



[A] *m*CPBA (2 eq), $BF_3 \cdot Et_2O$ (3 eq), AcOH, r.t., 43–63% yield, $R'' = OAc$.

[B] *m*CPBA (1.1 eq), *p*TsOH (1.1 eq), MeCN, 50 °C, 63–88% yield, $R'' = OTs$.

Scheme 3 First catalytic reactions using iodoarene as catalysts.

4.3.1.1 Task

No enantioselective catalytic α -oxysulfonylation reactions are known to date. Asymmetric iodine compounds synthesised during this project were to be employed as catalysts in the α -oxysulfonylation of phenones based on conditions shown above in order to achieve enhanced enantioselectivity, since now a much greater range of chiral iodine compounds can be employed.

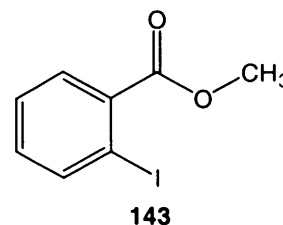
4.3.2 Results and Discussion

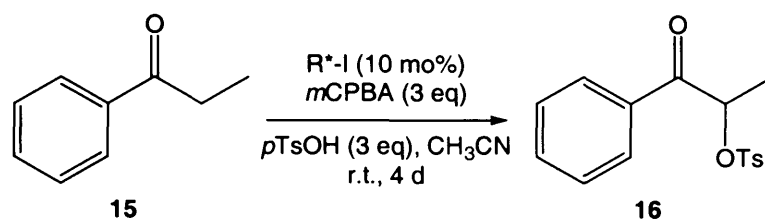
4.3.2.1 Propiophenone and *p*-Toluenesulfonic Acid

In order to optimise the enantioselectivities of the α -oxysulfonylation of propiophenone, firstly, a range of different iodoarenes was employed (Table 1). The reactions were conducted at room temperature for 2–4 days using commercial 70–77% wet *m*CPBA since no difference in the reactivity in comparison to the use of dried *m*CBPA was found previously. Acetonitrile was used as solvent, since this resulted in highest reaction rates as well as cleanest products as determined by Wirth and co-workers.^[18] The reactions were conducted at room temperature, since the reaction progress at $-30\text{ }^{\circ}\text{C}$ is very slow. It is assumed, that the oxidation of the iodoarene is the rate determining step in the catalytic cycle since the reaction proceeds readily at $-30\text{ }^{\circ}\text{C}$ with preformed hypervalent iodine reagents.^[18] In a next series of experiments, the nature of nucleophiles was examined. A range of sterically different sulfonic acids was employed. Finally, different phenones were used as starting materials, which have given promising results before.^[18,19]

Initially, *p*-toluenesulfonic acid was used as the nucleophile and clean reactions with propiophenone **15** to give tosylate **16** were observed. Most reactions were conducted using very small amounts of reagents such as 20 mg of propiophenone, leading to sometimes poor yields compared to conversions achieved due to loss during work-up and purification.

When terpene esters **60a–60c** derived from 2-iodobenzoic acid were used as catalysts, conversions and enantiomeric excess were quite poor; probably because the bulky ester moiety of **60a–60c** so close to the iodine atom might block the iodine centre from the reaction with oxidising agents resulting in poor reaction conversions (entries 1–3).^[19] This assumption is supported by the fact that firstly, esters **45c–45e** containing an additional carbon atom in the side chain resulted in excellent conversions. Here, the bulky terpene moiety is shifted further away from the iodine atom. Secondly, the commercially available non-chiral methyl ester **143** also gave good conversions (entry 4); the methyl moiety is too small to take effect on the oxidation of the iodine atom.





Entry	R [*] -I	R [*]	ee (%) ^b	Conversion (%) ^a	Yield (%)
1		60a ((-)-Bornyl)	1 (<i>S</i>)	8	8
2		60b (L-Menthyl)	3 (<i>S</i>)	8	6
3		60c ((+)-Fenchyl)	1 (<i>S</i>)	n.d.	5
4		143 (Methyl)	-	99	n.d.
5		45c ((-)-Bornyl)	6 (<i>S</i>)	n.d.	60
6		45d (L-Menthyl)	0	100	78
7		45e ((+)-Fenchyl)	0	100	84
8		45f (Helmchen)	-	0	0
9		(-)- 46a R = Me, R' = H	24 (<i>S</i>)	95	72
10		(-)- 46b R = Et, R' = H	23 (<i>S</i>)	95	83
11		(-)- 46c R = Bn, R' = H	6 (<i>S</i>)	n.d.	65
12		(-)- 47b R = Me, R' = <i>n</i> Pr	8 (<i>R</i>)	75	24
13		(2R)- 46e ((-)-Bornyl)	23 (<i>S</i>)	45	n.d.
14		(2R)- 46f (L-Menthyl)	15 (<i>S</i>)	n.d.	73
15		(2R)- 46g ((+)-Fenchyl)	26 (<i>S</i>)	100	n.d.
16		(2S)- 46e ((-)-Bornyl)	21 (<i>R</i>)	46	n.d.
17		(2S)- 46f (L-Menthyl)	39 (<i>R</i>)	100	42
18		(2S)- 46g ((+)-Fenchyl)	29 (<i>R</i>)	n.d.	67

^a determined by ¹H NMR analysis of the crude reaction product.

^b determined by HPLC.

n.d. not determined.

Table 1 (continued on next page)

Enantiomerically pure iodoaryl esters and ethers as catalysts in the α -oxytosylation of propiophenone **15**.

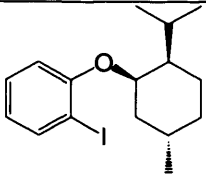
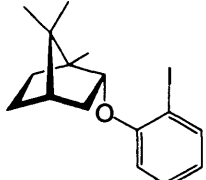
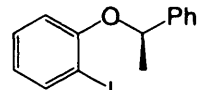
Entry	R*-I		ee (%) ^b	Conversion (%) ^a	Yield (%)
19		73a	1 (<i>R</i>)	97	9
20		73b	0	63	10
21		73c	4 (<i>R</i>)	22	11
a	determined by ¹ H NMR analysis of the crude reaction product.				
b	determined by HPLC.				
n.d.	not determined.				

Table 1 (continued) Enantiomerically pure iodoaryl esters and ethers as catalysts in the α -oxytosylation of propiophenone **15**.

However, an elongation of the side chain by one methylene moiety resulted in better conversions and yields, but still poor selectivities were observed when bornyl ester **45c** (entry 5) was employed and in racemic products when menthyl or fenchyl esters **45d** and **45e** (entries 6, 7) were used. Ester **45f** derived from an alcohol developed by Helmchen and co-workers failed completely to catalyse the reaction (entry 8). Possibly, the iodine atom is hindered by the bulky chiral moiety thus retarding the oxidation of the iodine atom.

As the introduction of stereogenic centres in the benzylic position of such reagents has already been successful as shown in Scheme 2. It was thought, that an increase of enantioselectivity could be achieved by alkylation of the prochiral esters **45c–e**, since the chiral centre would be closer to the iodine moiety. Firstly, different substituted methyl esters were tested in order to determine the optimal nature of the substituent; esters **46a–c** are furnished with one substituent (entries 9–11) whereas ester **46b** contains two substituents (entries 10–12). Conversions achieved were generally high. Highest enantioselectivities were observed, when catalyst **46a** containing one methyl substituent was employed. Esters **46b–c** and **47b** equipped with more hindered substituents or with even two substituents resulted in lower enantioselectivities (entry 12).

Based on these results, methyl substituents were introduced into esters **45c–e** by alkylation using LDA as base together with methyl iodide. The resulting diastereomers of esters **46e–g** were resolved by preparative HPLC. For time reasons, the other esters could not

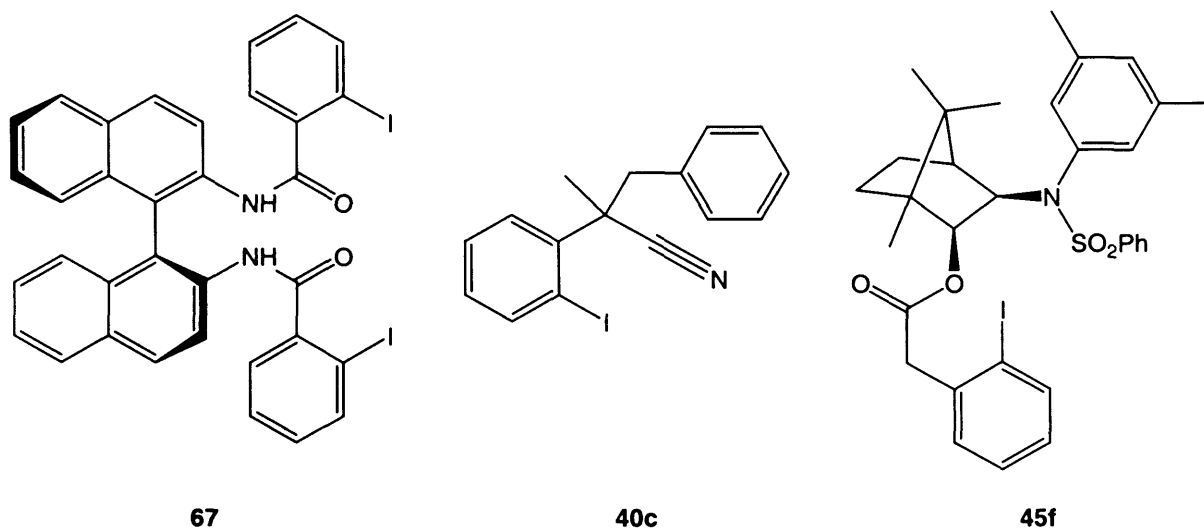
be transformed into the respective aryl alcohols. On the other hand, all products of the catalysed oxytosylation reaction appeared to have the same configuration, when catalysts of similar HPLC fractions were employed. For example, the first fraction of **46f** collected from the preparative HPLC was reduced to the respective phenylpropanol using LiAlH_4 and was determined to possess (*S*)-configuration by optical rotation and HPLC analysis compared to the generic phenylpropanol; the α -tosylated phenone **16** resulting from the reaction employing (2*S*)-**46f** as catalyst was (*R*)-configured. Generally, when the first HPLC fractions of **46e–g** resulted in (*R*)-configured **16** and the second HPLC fractions of **46e–g** in the respective (*S*)-configured **16**. This consistency prompts to the assumption, that these fractions have similar configurations, thus leading to similarly configured products.

When diastereomers of **46e–g** (entries 13–18) were employed as catalysts, an increase of enantioselectivity up to 39% was observed for the menthyl ester **46f** with (2*S*)-configuration at in the benzylic position (entry 17). On the other hand, the corresponding (2*R*)-diastereomer only resulted in 15% *ee* (entry 14). Without the additional methyl substituent in the benzylic position, the ester can rotate freely and no selectivity is observed. The methyl substituent might then force the ester into a certain conformation with the chiral terpene substituent leading to additional interactions. This results in lower selectivities (15% *ee*, entry 14), or in a ‘matched’ scenario, to higher selectivities (39% *ee*, entry 17) compared to the methyl ester **46a** (24% *ee*, entry 9). These facts again demonstrate the importance of a chiral moiety in *ortho*-position to iodine. The respective methyl substituted bornyl- and fenchyl esters **46e** and **46g** did not result in comparable enantioselectivities; even the differences between diastereomers (entries 13/16, 15/18) are not very high.

Ethers of 2-iodophenol **73a–73c** with various terpene-derived chiral moieties bearing no additional heteroatom resulted in almost no enantioselectivity (entries 19–21). The existence of an additional heteroatom in the chiral moiety, which is able to coordinate to the iodine atom, seems to be a very important feature of these catalysts.

In order to investigate the influence of a nitrogen atom as potential coordination site to the iodine atom, several amide catalysts have been prepared. Binaphthalene derivative **67** resulted in very poor yields and selectivities (Table 2, entry 1). Nitrile **40c** as catalyst resulted in good conversion (95%, entry 2), although the selectivity obtained is low (7% *ee*), probably due to poor coordination of the nitrogen atom to the iodine atom, so that the side chain can rotate freely rather than forming a rigid system. Compound **45f** also contains a nitrogen atom, that could coordinate to the iodine atom, but – as mentioned before – failed as catalyst; no conversion was observed (entry 3).





Entry	R*-I	ee of 16 (%) ^a	Conversion of 16 (%) ^b
1	67	2 (<i>S</i>)	7 ^c
2	(+)-40c	7 (<i>R</i>)	95
3	45f	-	0

^a determined by HPLC
^b determined by ¹H NMR
^c yield (%)

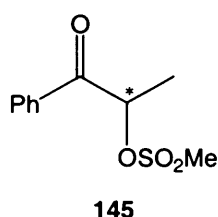
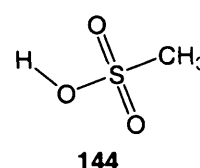
Table 2 Nitrogen-containing iodoarenes as catalysts in the α -oxytosylation of propiophenone.

The fact, that disubstituted esters and nitriles as catalysts only result in poor enantiomeric excess, confirms the crucial influence of non-bulky substituents in the side chain, as observed previously.^[20]

4.3.2.2 Different Sulfonic Acids

Having determined the most promising chiral esters as suitable catalysts, now the nature of nucleophiles was examined in order to achieve higher enantioselectivities. A range of different sterically hindered as well as chiral sulfonic acids was employed.

Methanesulfonic acid **144** was used as least sterically hindered reagent (Table 3). Conversions were generally much poorer than conversions of reactions using *p*TsOH, whereas enantioselectivities decreased only little. Other than in reactions mention above, menthyl-derived ester **60b** did not result in the formation of ketone **145** (entry 1), on the other hand, this reaction was done only once and should be repeated. Methyl-substituted ester **46a** catalysed the reaction in moderate results with 23% *ee* and 33% conversion (entry 2). The respective ethyl-substituted ester **46b** gave poor conversions as well as poor enantioselectivity (entry 3). Once more, highest enantioselectivity was achieved by employment of (2*S*)-menthyl ester (2*S*)-**46f** (31% *ee*, entry 4), whereas conversions were only moderate 39%. The respective (2*R*)-diastereomer only achieved 15% *ee* (entry 5) and 26% isolated yield of product **145**. Terpene ethers **73a** and **73b** both resulted in poor enantioselectivity of 5 and 2%; **73a** catalysed the reaction in good conversions of 85%, whereas **73b** only achieved 13% (entries 6, 7). Best conversions were observed when ether **73c** was employed; enantioselectivity on the other hand was poor (entry 8).

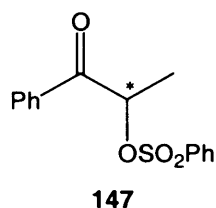
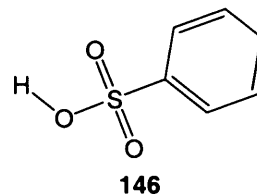


Entry	R*-I	<i>ee</i> (%) ^a	Conversion (%) ^b [Yield]
1	60b	-	0
2	(-)- 46a	23	33
3	(-)- 46b	18	5
4	(2 <i>S</i>)- 46f	31	39
5	(2 <i>R</i>)- 46f	15	[26]
6	73a	5	85
7	73b	2	13
8	73c	4	89

^a determined by HPLC.
^b determined by ¹H NMR analysis of the crude reaction product.

Table 3 Methanesulfonic acid **144** as nucleophile.

The employment of bulkier benzenesulfonic acid **146** also resulted in decrease of enantioselectivities (Table 4) of sulfonylated product **147** compared to products of employment of *p*-toluenesulfonic acid. Menthyl ester **60b** furnished with a short side chain in *ortho*-position to the iodine atom gave only traces of ketone **147**; enantioselectivity was not determined. Conversions and selectivities achieved using ester **46a** differed only little from results gained from the use of *p*-toluenesulfonic acid (entry 2), whereas ester **46b** gave improved enantioselectivity and conversion compared to the results achieved from the employment of *p*-toluenesulfonic acid (entry 3); similar values were achieved with employment of **46a**. The (2*S*)-diastereomer of menthyl-derived ester **46f** on the other hand resulted in slightly decreased enantioselectivity (20% *ee*, entry 4), but only poor conversion of 15% was detected. The corresponding (2*R*)-diastereomer resulted once more in minor enantioselectivity (18%, entry 5), whereas excellent conversion of 100% was observed. Terpene ethers **73a** and **73b** achieved only moderate conversion of 33% and 50%, but only racemic products were obtained. Ether **73c** only resulted in poor conversion of 20% and nearly racemic product **147** (2% *ee*, entry 8).



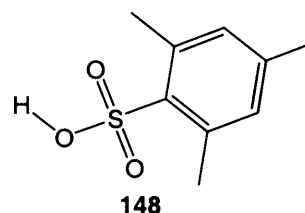
Entry	R ⁺ -I	<i>ee</i> (%) ^a	Conversion (%) ^b	Yield (%)
1	60b	n.d.	<5	n.d.
2	(+)-46a	23	89	13
3	(+)-46b	22	98	80
4	(2<i>S</i>)-46f	29	15	n.d.
5	(2<i>R</i>)-46f	18	100	47
6	73a	0	50	n.d.
7	73b	0	33	n.d.
8	73c	2	20	n.d.

^a determined by HPLC.

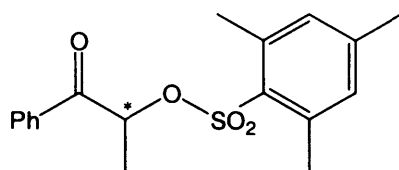
^b determined by ¹H NMR analysis of the crude reaction product.

Table 4 Benzenesulfonic acid **146** as nucleophile.

Mesitylenesulfonic acid **148** was employed as more sterically congested nucleophile yielding ketone **149** (Table 5). Catalyst **60b** failed to give any product (entry 1). Surprisingly, (2*R*)-diastereomer of **46f** yielded in higher enantioselectivity alongside moderate conversion (entry 3), whereas respective (2*S*)-diastereomer of **46f** showed good conversion



but very poor selectivity (entry 2). Also, reactions catalysed by fenchyl-derived catalyst (*2R*)-**46g** were conducted, resulting in only moderate selectivity of 22% and poor conversion (10%, entry 4).



149

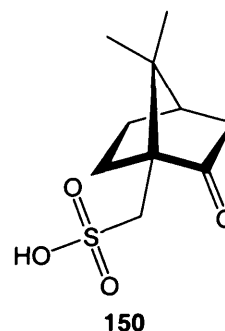
Entry	R*-I	ee (%) ^a	Conversion (%) ^b	Yield (%)
1	60b	-	0	0
2	(<i>2S</i>)- 46f	11	100	33
3	(<i>2R</i>)- 46f	29	20	17
4	(<i>2R</i>)- 46g	22	10	9

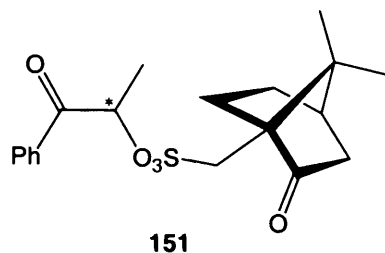
a determined by HPLC.

b determined by ¹H NMR analysis of the crude reaction product.

Table 5 Mesitylenesulfonic acid **148** as nucleophile.

It was thought, that chiral sulfonic acids such as camphorsulfonic acids employed as nucleophiles could lead to increased diastereoselectivities (Table 6). This was indeed the case; the use of (*1S*)-camphorsulfonic acid **150** as nucleophile increased the diastereoselectivity up to 44% when the reaction was catalysed by diastereomer **46f** with (*2S*)-configuration in the benzylic position (entry 3), alongside moderate conversion of 67%. The respective (*2R*)-diastereomer of **46f** as well as fenchyl ester (*2R*)-**46g** obtained only mediocre selectivities of 26% de and 25% de (entries 4,5). Catalysts **60b** and **46a** failed to yield product **151** (entries 1,2).





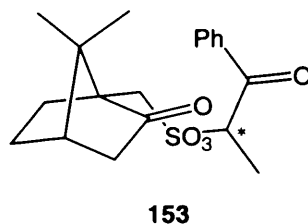
Entry	R ⁺ -I	de (%) ^a	Conversion (%) ^b	Yield (%)
1	60b	n.d.	n.d.	n.d.
2	(-)-46a	n.d.	n.d.	n.d.
3	(2S)-46f	44	67	24
4	(2R)-46f	26	71	28
5	(2R)-46g	25	43	23

a determined by HPLC.

b determined by ¹H NMR analysis of the crude reaction product.

Table 6 (1S)-(+)-Camphorsulfonic acid **150** as nucleophile.

Also, the respective (1R)-camphorsulfonic acid **152** was employed as nucleophile alongside both diastereomers of **46f** as catalysts in order to investigate the influence of the opposite diastereomer nucleophile (Table 7). (2S)-**46f** gained 34% *ee*, whereas the (2R)-diastereomer of **46f** resulted in 18% *de* of product **153**.



Entry	R ⁺ -I	de (%) ^a	Conversion (%) ^b	Yield (%)
1	(2S)-46f	34	100	10
2	(2R)-46f	18	n.d.	18

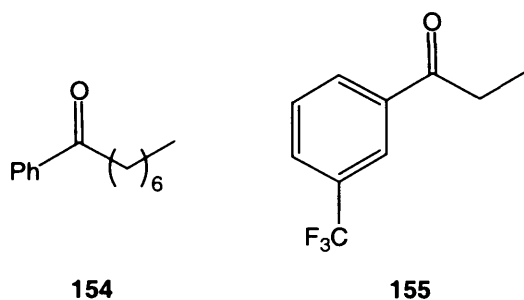
a determined by HPLC.

b determined by ¹H NMR analysis of the crude reaction product.

Table 7 (1R)-(-)-Camphorsulfonic acid **152** as nucleophile.

4.3.2.3 Different Ketones

After determination of the so far best catalyst and nucleophile, different aromatic ketones were employed, which achieved promising results in the past.^[18] Based on these results, catalyst (2*S*)-**46f**, which has in the past provided highest enantioselectivities, was employed in reactions together with (1*S*)-camphorsulfonic acid as nucleophile and octanophenone **154** (Table 8, entry 1) or *m*-(trifluoromethyl)propiophenone **155** (entry 2), respectively. Enantioselectivities and conversions were inferior to the results achieved by *p*TsOH and other catalysts (16 and 26% *ee*).



Entry	Product	de (%) ^a	Conversion (%) ^b	Yield (%)
1	 156	16	24	23
2	 157	26	52	19

^a determined by HPLC.

^b determined by ¹H NMR analysis of the crude reaction product.

Table 8 (1*S*)-(+)-Camphorsulfonylation of selected ketones catalysed by (2*S*)-**46f**.

Up to now, in most cases the iodine atom was bound covalently to a benzene moiety in hypervalent compounds. To our best knowledge, the only alkyl iodides oxidised to λ^3 -iodanes are fluorinated iodine compounds,^[21-24] also, vinyl iodides have been oxidised.^[25] Iodoalkanes containing a very small alkyl moiety cannot be isolated as hypervalent compounds due to

their low stability. Now, methyl iodide (table 9, entry 1) and iodoacetonitrile (entry 2) were employed as catalysts in the α -oxytosylation of propiophenone. The reaction using methyl iodide as catalyst gave mediocre conversion of 18% and iodoacetonitrile failed to catalyse this reaction.

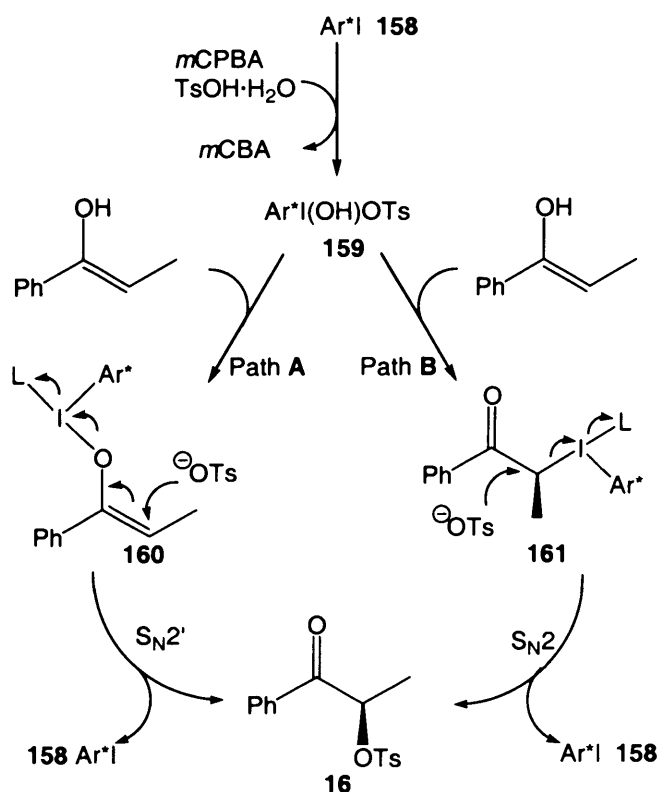
Entry	R-I	Conversion of 16 (%) ^a
1	CH ₃ -I 123	18
2	NCCH ₂ I 86	0

a determined by ¹H NMR analysis of the crude reaction product.

Table 9 Alkyl iodides as catalysts in the α -oxytosylation of propiophenone.

4.3.2.4 Reaction Mechanism

Two possible mechanisms are discussed for the α -oxytosylation of propiophenone catalysed by iodoarenes (Scheme 4). The enol tautomer of propiophenone reacts with the Koser-type iodane **159** generated *in situ* from iodoarene **158** (path A); subsequent S_N2'-type attack of the tosylate replaces the iodine moiety. The facile reduction of λ^3 -iodane to an iodine(I) compound in the reductive elimination step forms the driving force for this reaction.^{[15],[26]}



Scheme 4 Possible mechanisms for the catalytic α -oxytosylation of ketones.

Another mechanistical possibility is the hypervalent iodine atom to be attacked by the double bond electrons of the enol tautomer to form **161** with subsequent S_N2-type replacement by the tosylate (path **B**). The fact that the chiral moiety in intermediate **161** is closer to the stereo centre formed than it would be in **160** corresponds to the enantioselectivities achieved in this reaction. This supports the assumption of path **B** taking place; concordantly to the mechanism proposed by *Moriarty*.^[27]

In this reaction, substitution of the hyperleaving group by *m*-chlorobenzoate rather than by the tosylate does not occur in our work as well as that of *Togo*.^[17] Also, enolisation of product **16** resulting in racemisation, which is vital take place in propiophenone **15** in order to proceed the reaction, has not been monitored. To ensure this fact, enriched product **16** was resubmitted to the reaction conditions described above; no change of enantioenrichment was observed. The results obtained fortify the suggestion, that a rigid 5-membered ring is formed in the hypervalent species based on oxygen-containing catalysts. In here, the chiral centre is fixed in position due to coordination to the iodine atom, yielding moderate enantioselectivities. If this interaction cannot be formed, free rotation of the chiral moiety is possible resulting in poor enantioselectivities.

4.3.2.5 Conclusion

In conclusion, the enantioselective oxysulfonylation of ketones catalysed by enantiomerically pure iodoarenes has been established and improved. α -Sulfonylated ketones were obtained in good yields as well as promising enantiomeric and diastereomeric excesses. Best results were achieved, when esters containing two chiral centres were used as catalysts and a chiral sulfonic acid used as nucleophile. In addition, we demonstrated, that not only iodoarenes can be applicable as catalysts but also some alkyl iodides, thus enlarging the range of possible iodocatalysts considerably.

4.3.3 Literature

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5 Experimental Section

5.1 General Methods

Most reactions were carried out using standard laboratory equipment. Air-insensitive reactions were conducted in loosely covered vials; inert reactions were conducted in reduced pressure-dried and heat gun heated or oven dried (120 °C) glassware under argon atmosphere. All reactions were agitated by magnetic stirring and – when needed – warmed to defined constant temperatures by hotplates with temperature probe control in silicon oil or dry heating blocks. Büchi B-461, B-481 or B-490 rotary evaporators (reduced pressure down to ca. 15 mbar) were used for solvent evaporations; further drying was undertaken by the use of a high vacuum apparatus. A Büchi GKR-50 Kugelrohr distillation apparatus was employed for Kugelrohr distillations. For inert reactions, freshly over drying agents and under inert atmosphere distilled anhydrous solvents were used: CH₂Cl₂ over calcium hydride and THF over sodium and benzophenone. All other high purity solvents used were purchased from Aldrich, Alfa Aesar, Fluka or Acros in septum bottles with inert atmosphere. Reactions performed at low temperatures were stirred in vessels cooled in a dry ice/acetone bath (–78 °C), ice/water/NaCl bath (–15 °C) or ice/water bath (0 °C).

5.2 Physical Data

¹H NMR spectroscopy

Bruker DPX 500 (500 MHz), DPX 400 (400 MHz) or Bruker DPX 250 (250 MHz).

The chemical shifts δ are given in ppm downfield of tetramethylsilane ($\delta = 0$ ppm). Compounds and crude reaction mixtures are dissolved in either deuterated chloroform or deuterated dimethylsulfoxide. Coupling constants are given in Hertz. The multiplicity of signals is designated: s = singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, m = multiplet and aromatic for aromatic ring protons, which could not be assigned. Solvent peaks are assigned as follows: 7.26 ppm for CHCl₃, 2.54 ppm for DMSO.

The numbering of the molecules in the respective diagrams is not according to the IUPAC convention but corresponds to the proton resonances.

¹³C NMR spectroscopy

Bruker DPX 500 (125 MHz), Bruker DPX 400 (100 MHz) or DPX 250 (62.5 MHz).

The chemical shifts δ are given in ppm downfield of tetramethylsilane. Compounds and crude reaction mixtures are dissolved in either deuterated chloroform or deuterated dimethylsulfoxide. Solvent peaks are assigned as follows: 77.36 ppm for CDCl₃, 40.45 ppm for DMSO.

Mass Spectrometry

Waters LCR Premier XE – tof

Mass spectroscopic measurements have been performed by R. Jenkins, R. Hicks or D. Walker at Cardiff University and also EPSRC MS Service Centre, Swansea University. Ions were generated by the atmospheric pressure ionisation techniques voltage applied corona discharge pin (APCI), voltage on a tip (ES) or electronical ionisation (EI). Mass fragments usually are given in atomic mass units per elementary charge (m/z). The intensity relative to the strongest signal is quoted in brackets using percentages. High resolution mass spectrometry for some compounds was carried out by EPSRC Swansea. All molecular formulae are values quoted for either molecular ions (M^{+}), molecular + hydrogen ($M + H^{+}$) or molecular + ammonium ion ($M + NH_4^{+}$).

Gas Chromatography Mass Spectrometry

Perkin Elmer 8700, *beta*-column

High Pressure Liquid Chromatography

Shimadzu Class VP (SIL-10ADVP auto injector, LC-10ATVP liquid chromatograph, FCV-10ALVP, DGU-14A degasser, CTO-10ASVP column oven, SCL-10AVP system controller, SPD-M10A diode array detector)

Only solvents of HPLC grade purity were used (usually 2-propanol and hexane). Analytical chiral columns (0.46 cm Θ x 25 cm) were used for separation of enantiomers (Chiracel OB, OB-H, OD-H, AD) at solvent flow rates of 0.5 mL/min; for preparative separations of enantiomers a chiral preparative Chiracel OD column (2 cm Θ x 25 cm) was used, the solvent flow rate was 3 mL/min.

IR Spectroscopy

Perkin Elmer 1600 series FTIR

Wave numbers are quoted in cm^{-1} ; samples were measured either neat or as KBr disc.

Chromatography

Merck Kieselgel 60 silica (230–400 mesh) was used for flash column chromatography. Thin layer chromatography (TLC) was performed on aluminium plates pre-coated with Merck Kieselgel 60 F254 and visualised by UV radiation or by staining with ceric ammonium molybdate.

Melting Point

Gallenkamp variable heater

Melting points were measured in open capillary tubes. All melting points taken are uncorrected.

5.3 General Procedures

GP1 Etherification of 1-Fluoro-2-nitrobenzene^[1]

In a dry flask 2.2 eq of sodium hydride (60% in mineral oil, 5.6 mmol) were washed with hexane to remove the mineral oil and then dried by flushing with argon. The resulting powder was suspended in dry THF. Then 1.0 eq of 1-fluoro-2-nitrobenzene (2.54 mmol, 358.3 mg) in THF were added dropwise at 0 °C. Subsequently 2.2 eq of an alcohol (5.6 mmol) were added and the mixture was refluxed over night. The mixture was washed with aqueous saturated NH_4Cl solution (8 mL), extracted with CH_2Cl_2 (5 x 6 mL) and dried over MgSO_4 . After filtration and evaporation of the solvents the product was purified by column chromatography (petroleum ether:diethyl ether 4:1).

GP2 Hydrogenation of Nitroarenes^[2]

The respective nitroaryl ether (0.9 mmol) was dissolved in MeOH (40 mL) in a flask under argon atmosphere. Then Pd/C (10%, 8 mg) was added and the mixture was stirred vigorously in hydrogen atmosphere for 4–6 hours. The mixture was then filtered through SiO_2 and the solvent was evaporated; the crude product was used without further purification.

GP3 Iodination of Amines^[3]

To a mixture of an amine (1 eq, 1.02 mmol) in water and conc. H_2SO_4 a solution of sodium nitrite (1.2 eq, 1.36 mmol, 94 mg) was added slowly at 0 °C and the mixture was stirred for 3 d. After reaction completion the excess nitrous acid was quenched by the addition of urea. Then an aqueous solution of KI (1.2 eq, 1.36 mmol, 225.8 mg) was added and the mixture was stirred for 3 h at 50 °C. To the resulting mixture an aqueous saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) was added. The mixture was extracted with diethyl ether (5 x 5 mL), washed with 1 M NaOH to pH 5, washed with brine and dried over MgSO_4 . After filtration, evaporation of the solvent under reduced pressure afforded the crude product.

GP4 Synthesis of Esters

2-Iodobenzoyl chloride or (2-iodophenyl)acetic acid (1 eq, 1.2 mmol) and an alcohol (1.5 eq, 1.8 mmol) were stirred together with *p*TsOH (5 mol%, 0.06 mmol) in acetonitrile or CH_2Cl_2 at r.t. or at enhanced temperature up to 80 °C (depending on reaction progress monitored by TLC) for 1–3 d. After reaction completion, the mixture was allowed to cool to room

temperature and poured into aqueous saturated NaHCO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried over MgSO_4 and solvent was removed after filtration. The crude product was purified by flash chromatography (petroleum ether:diethyl ether 4:1).

GP5 Alkylation of Esters and Nitriles^[4]

To a freshly prepared LDA solution (1.2 eq, 1.8 mmol) was added dropwise a solution of the respective iodoarene ester or iodoarene nitrile (1 eq, 1.5 mmol) in dry THF at -78°C and stirred for 30 minutes at this temperature. Then MeI (1.2 eq, 1.8 mmol) was added dropwise and the mixture was stirred at room temperature for 2–3 h. After reaction completion, the mixture was poured into aqueous saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried over MgSO_4 and solvent was removed after filtration. If the ester or nitrile was alkylated twice, the procedure was repeated with the crude reaction mixture without further purification. The crude product was purified by flash chromatography (petroleum ether:diethyl ether 4:1).

GP6 Synthesis of Amides

2-Iodobenzoyl chloride (3 eq, 3.2 mmol) and the respective amine (1 eq, 1.07 mmol) were stirred in CH_2Cl_2 at room temperature for 2 d. After reaction completion, the mixture was poured into aqueous saturated NaHCO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried over MgSO_4 and solvent was removed after filtration. The crude product was purified by flash chromatography (petroleum ether:diethyl ether 4:1).

GP7 α -Oxysulfonylation of Ketones^[5,6]

A ketone (1 eq, 0.1 mmol), an organoiodine catalyst (10 mol%, 0.01 mmol), *m*CBPA (3 eq, 0.3 mmol) and a sulfonic acid (3 eq, 0.3 mmol) were stirred at room temperature for 2–4 d. After reaction completion, the mixture was poured into aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ (6 mL) and extracted with CH_2Cl_2 (3 x 5 mL). Then, the organic layers were poured into aqueous saturated NaHCO_3 (6 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed after filtration. The crude product was purified by flash chromatography (petroleum ether:diethyl ether 4:1).

GP8 α -Acetoxylation of Propiophenone^[7]

Propiophenone (1 eq, 0.1 mmol), an organoiodine catalyst (10 mol%, 0.01 mmol), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3 eq, 0.3 mmol) and acetic acid (3 eq, 0.3 mmol) were stirred at room temperature for 2–4 d. After reaction completion, the mixture was poured into aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ (6 mL) and extracted with CH_2Cl_2 (3 x 5 mL). Then, the organic layers were poured into aqueous saturated NaHCO_3 (6 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed after filtration. The crude product was purified by flash chromatography (petroleum ether:diethyl ether 4:1).

GP9 Bromolactonisation of Pentenoic acids^[8]

A pentenoic acid (1 eq, 0.1 mmol) was stirred together with an organoiodine catalyst (10 mol%, 0.01 mmol) and freshly recrystallised white NBS (1 eq, 0.1 mmol) in chloroform for 1–3 d. Then, solvent was evaporated and a crude NMR was taken. Purification was done by preparative TLC (petrol ether:diethyl ether 2:1).

GP10 Oxidation of Iodoarenes using NaOCl ^[9]

CH_2Cl_2 was added to a vigorously stirred suspension of an iodoarene (1 eq, 0.5 mmol) and sodium hypochlorite solution 4% (2 mL) and then acetic acid (0.5 mL) was added dropwise in 10 min at room temperature. The resulting mixture was stirred overnight. The iodoxy compounds were extracted from the reaction mixture with CH_2Cl_2 (5 x 10 mL). The extract was washed with aqueous saturated NaHCO_3 solution (6 mL), dried over MgSO_4 and the solvent was evaporated under reduced pressure after filtration to afford the crude product.

GP11 Oxidation of Iodoarenes using DMDO^[10]

An iodoarene is stirred in a solution of DMDO (1–3 eq, depending on reaction progress) in acetone at room temperature for 8 h. After reaction completion, the solvent is evaporated and the resulting solid is washed with diethyl ether.

GP12 Oxidation of Iodoarenes using DMP

To a stirred solution of an iodoarene ester (1 eq, 0.525 mmol) in CH_2Cl_2 (3 mL) Dess-Martin periodinane (2 eq, 1.05 mmol) was added carefully and the mixture was stirred for 2 ½ h at room temperature. Then distilled water (5 mL) and CH_2Cl_2 (5 mL) were added, the mixture stored in fridge over night and emerged solid filtered and dried under reduced pressure.

GP13 Oxidation of Iodoarenes using NaIO₄^[11]

To sodium periodate (1.54 eq, 0.81 mmol) in distilled water (1 mL) an iodoarene ester (1 eq, 0.525 mmol) in methanol (1 mL) was added and stirred for 72 h at room temperature. The mixture was extracted with CH₂Cl₂ (5 x 5 mL) and dried over MgSO₄. The solvent was evaporated after filtration.

GP14 Oxidation of Iodoarenes using *m*CPBA^[12]

To a stirred solution of an iodoarene ester of (2-iodophenyl)acetic acid (1 eq, 0.5 mmol) in CH₂Cl₂ (50 mL) and acetic acid (50 mL) *m*CPBA (1.2 eq, 6 mmol) was added and stirred for 72 h at room temperature. The mixture was poured into aqueous saturated NaHCO₃ (6 mL) and extracted with CH₂Cl₂ (5 x 5 mL), the organic phase washed with brine (5 mL) and dried over MgSO₄. The mixture was stored in fridge and emerging solid was filtered, washed with CH₂Cl₂ and dried under reduced pressure.

GP15 Oxidation of Iodoarenes using KBrO₃^[13]

To a stirred solution of the respective derivative of (2-iodophenyl)acetic acid (1 eq, 0.82 mmol) in concentrated sulfuric acid (12.2 mL) potassium bromate (1.5 eq, 1.2 mmol) was added slowly and the mixture stirred at 60 °C for 10 h. After cooling to room temperature distilled water (5 mL) was added and the mixture extracted with CH₂Cl₂ (5 x 9 mL) and dried over MgSO₄ followed by filtration.

GP16 Oxidation of Iodoarenes using NaBO₃·4H₂O^[14]

Sodium perborate (10 eq, 8.25 mmol) was added portionwise to a stirred solution of the respective derivative of (2-iodophenyl)acetic acid (1 eq, 0.825 mmol) in CH₂Cl₂ (5 mL) and acetic acid (15 mL) and the mixture stirred at 60 °C for 24 h. Then distilled water (10 mL) was added and the mixture extracted with CH₂Cl₂ (5 x 5 mL) and dried over NaSO₄ followed by filtration.

GP17 Oxidation of Iodoarenes using Peracetic Acid^[15]

Peracetic acid (36–40% wt. in acetic acid, 12 mL) was added to a stirred solution of the respective derivative of (2-iodophenyl)acetic acid (1 eq, 1.5 mmol) in CH₂Cl₂ (4 mL) and stirred at room temperature for 12 h. After reaction completion, solvent and peracetic acid were evaporated.

GP18 Manipulation of Nitriles via Grignard Reaction^[16]

To Mg (2.1 eq, 0.581 mmol) in a dry flask was added dry benzene/diethyl ether (1/1, v) (5 mL) and methyl iodide (2 eq, 0.553 mmol) was added dropwise until start of reaction. Then (2-iodophenyl)acetonitrile (1 eq, 0.277 mmol) in dry benzene/diethyl ether (1/1, v) (1.5 mL) was added carefully and stirred at 30 °C for 24 h. Then the mixture was poured onto crushed ice (0.5 g) and 1 M HCl (1.5 mL), phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The extract was dried over MgSO₄ and the solution was filtered.

GP19 Manipulation of Nitriles using NaOH^[17]

To (2-iodophenyl)acetonitrile (1 eq, 2.315 mmol) in methanol (4 mL) was added sodium hydroxide (5 eq, 11.57 mmol) and this mixture refluxed for 3 h. Then H₂O_{dist.} (3 mL) was added and the mixture extracted with CH₂Cl₂ (5 x 5 mL) and dried over MgSO₄ followed by filtration of the solution.

GP20 Manipulation of Nitriles using HCl^[18]

To (2-iodophenyl)acetonitrile (1 eq, 0.25 mmol) in methanol (2 mL) was added hydrochloric acid (≥ 32%, 200 µl) and this mixture was stirred at 40–55 °C for 48 h. Then H₂O_{dist.} (3 mL) was added and the mixture extracted with CH₂Cl₂ (5 x 5 mL) and dried over MgSO₄.

GP21 Manipulation of Nitriles using TMSCl/MeOH^[19]

Methanol (2 eq, 0.55 mmol), trimethylsilylchloride (4.3 eq, 1.18 mmol) and (2-iodophenyl)-acetonitrile (1 eq, 0.272 mmol) were sequentially added to a dry flask with inert atmosphere and stirred at 50 °C for 48 h. After cooling to room temperature H₂O_{dist.} (0.1 mL) was added followed by addition of aqueous saturated Na₂CO₃ (0.1 mL) and extracted with CH₂Cl₂ (5 x 3 mL) and dried over MgSO₄.

GP22 Manipulation of Nitriles using KOH/Ethylene Glycol^[20]

(2-Iodophenyl)acetonitrile (1 eq, 0.35 mmol) and potassium hydroxide (7.8 eq, 2.73 mmol) were stirred in ethylene glycol (5 mL) at 105 °C for 16 h. The hot solution was poured onto ice and extracted with CH₂Cl₂ (5 x 5 mL). The aqueous layer was acidified with 1 M hydrochloric acid (7 mL) and again extracted with hydrochloric acid (4 mL) and the combined organic layers dried over MgSO₄.

GP23 Manipulation of Nitriles using H₂SO₄^[21]

(2-Iodophenyl)acetonitrile (1 eq, 0.52 mmol) and sulfuric acid_{conc.} (>95%, 30 μ l) were stirred at 50 °C for 7 days. Then H₂O_{dist.} (4 mL) was added and the mixture extracted with CH₂Cl₂ (5 x 5 mL) and dried over MgSO₄.

GP24 Manipulation of Iodoarene Esters using TMSCl^[22]

Sodium iodide (1.5 eq, 0.63 mmol) was dried by heating reduced pressure. Then the ester of (2-iodophenyl)acetic acid (1 eq, 0.42 mmol), freshly distilled acetonitrile (3 mL) and trimethylsilyl chloride (1.5 eq, 0.63 mmol) were added and the mixture stirred at 45 °C for 2 h. Then H₂O_{dist.} (3 mL) was added and the mixture extracted with CH₂Cl₂ (3 x 5 mL) and dried over MgSO₄.

GP25 Manipulation of Iodoarene Esters using NaOH or LiOH^[23]

The ester of (2-iodophenyl)acetic acid (1eq, 0.763 mmol) was dissolved in THF/H₂O_{dist.} (50/50, v, 6 mL) and NaOH or LiOH (3 eq, 2.3 mmol) was added and the mixture stirred for 24 h at room temperature. THF was evaporated and the residue was dissolved in H₂O_{dist.} (3 mL) and acidified with 5 M hydrochloric acid to pH 2 and the mixture extracted with CH₂Cl₂ (3 x 8 mL) and dried over MgSO₄.

GP26 Oxidation of Sulfides and Alcohols^[24]

A sulfide (1.5 eq) was stirred in acetonitrile together with a iodoxy compound (1 eq) at 40–80 °C depending on reaction progress for 4h. For enhanced dissolving of iodoxy arenes, TFA (1 eq) can be added. The crude reaction mixture was poured onto saturated aqueous Na₂S₂O₃ and extracted with CH₂Cl₂ and the organic phase dried over Na₂SO₄.

GP27 Synthesis of Propiophenone Derivatives^[25]

Zirconocene dichloride (438.5 mg, 1.5 mmol) in a dry 2-necked Schlenk flask was heated under reduced pressure in order to remove water. Under argon atmosphere, dry THF was added and the mixture was cooled to –78 °C. *t*BuLi in hexane (1.5 M, 0.9 mL, 1.3 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for one hour. The reaction mixture was then again cooled to –78 °C. In a second dry 2-necked flask, a 4-bromide-3-ethylanisole (322.5 mg, 1.5 mmol) was dissolved in dry THF (2.5 mL) and cooled to –78 °C. To this solution, *n*BuLi (1.5 mmol, 0.6 mL, 2.5 M) in hexane was added dropwise and the mixture was allowed to warm to room temperature and stirred for 15 mins.

After cooling to $-78\text{ }^{\circ}\text{C}$, this mixture was added to the zirconocene mixture with a syringe and stirred at $-50\text{ }^{\circ}\text{C}$ for one hour. After addition of propionitrile (68.9 mg, 1.25 mmol), the reaction mixture was stirred at $65\text{ }^{\circ}\text{C}$ for 18h in a closed apparatus. After cooling to room temperature, iodine (793.2 mg, 3.13 mmol) in dry THF (3.2 mL) was added and the mixture stirred for 7h at this temperature. After hydrolysis with 1M HCl (2.6 mL) and stirring for 5h, the reaction mixture was extracted with aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (8 mL) and the organic phase washed with water and dried over MgSO_4 .

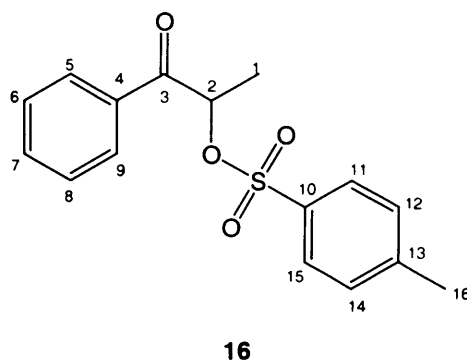
GP28 Reduction of Iodoarene Esters using LiAlH_4 ^[26]

To an ester (1 eq) dissolved in dry THF was added LiAlH_4 dissolved in dry THF at room temperature and the reaction mixture was stirred for 2 h. The reaction mixture was quenched with $\text{H}_2\text{O}_{\text{dist}}$ and aqueous 15% NaOH solution and extracted with CH_2Cl_2 (3 x 7 mL) and the organic phase dried over MgSO_4 followed by filtration and solvent evaporation under reduced pressure.

5.4 Characterisation of Compounds

(±)-2-*p*-Toluenesulfonylpropiophenone^[27] **16**

Synthesis according to GP7 from commercially available propiophenone (44.7 mg, 0.3 mmol), catalyst (*S*)-**46f** (10 mol%, 0.03 mmol, 13.8 mg), *m*CPBA (172.4 mg, 1.0 mmol, 3 eq) and *p*-toluenesulfonic acid (190.0 mg, 1.0 mmol, 3 eq). After work-up using saturated aqueous Na₂S₂O₃, saturated aqueous NaHCO₃ and extraction with CH₂Cl₂ (5 x 7 mL), the organic phase was dried over Na₂SO₄; purification by preparative TLC (diethylether:petrol ether 1:2).



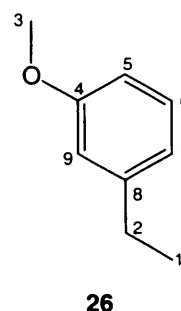
Yield: 42% (42.6 mg, 0.13 mmol), yellow oil.

¹H NMR (250 MHz, CDCl₃): δ (ppm) = 1.60 (d, 3H, *J* = 6.9 Hz, 1-CH₃), 2.41 (s, 3H, 16-CH₃), 5.79 (q, 1H, *J* = 6.9 Hz, 2-CH), 7.25–7.28 (m, 2H, aromatic), 7.42–7.49 (m, 2H, aromatic), 7.59 (tt, 1H, *J* = 7.4, 2.2 Hz, aromatic), 7.73–7.78 (m, 2H, aromatic), 7.85–7.90 (m, 2H, aromatic).

HPLC Separation: Chiracel OB-H column, 40:60 hexane:2-propanol, 0.5 mL/min, 40 °C, *t*_R = 18.1 min (*R*), 21.6 min (*S*).

3-Methoxyethylbenzene^[28] **26**

To a slurry of NaOH (799.8 mg, 20 mmol) in H₂O (4 mL) and an aqueous solution of tetrabutylammonium hydroxide (40%) (622 μl, 1 mmol) was added dropwise to a solution of 3-ethylphenol **25** (1.53 mL, 10 mmol) in H₂O (5 mL). To the resulting reaction mixture dimethylsulfate (1.5 g, 12 mmol) was added dropwise. After stirring for 2 hours, separation of the organic layer, extraction of the aqueous layer with CH₂Cl₂ (3 x 8 mL) followed. The combined organic layers were dried over MgSO₄ and the solvent was evaporated under reduced pressure after filtration. Purification was conducted by distillation (75 °C, 0.1 bar).



Yield: 91% (9.1 mmol, 1.24 g), colourless oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.14 (t, 3H, J = 6.9 Hz, 1- CH_3), 2.53 (q, 2H, J = 7.6 Hz, 2- CH_2), 3.68 (s, 3H, 3- CH_3), 6.65 (d, 1H, J = 8.1 Hz, 7- CH), 6.69 (s, 1H, 9- CH), 6.72 (d, 1H, J = 8.1 Hz, 5- CH), 7.1 (m, 1H, 6- CH).

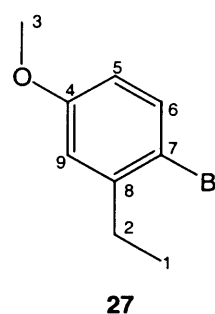
^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 15.9 (1-C), 29.4 (2-C), 55.5 (3-C), 111.2, 114.1, 120.7, 129.7, 146.3, 160.1 (4-C).

2-Ethyl-4-methoxybromobenzene^[28] **27**

A slurry of **26** (344 mg, 2.53 mmol) and iron filings (4.9 mg, 0.09 mmol) in FREON (8 mL) was stirred and cooled in an ice/salt bath as a solution of bromine (444.2 mg, 2.78 mmol) in FREON (4 mL) was added dropwise (slowly!). After 3 hours, the reaction mixture was poured into water. After addition of an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$, the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over MgSO_4 . After filtration and evaporation of the solvent under reduced pressure, purification was conducted by distillation (80 °C, 0.1 bar).

Yield: 89% (484.1 mg, 2.3 mmol), colourless oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.11 (t, 3H, J = 7.5 Hz, 1- CH_3), 2.60 (q, 2H, J = 7.4 Hz, 2- CH_2), 3.65 (s, 3H, 3- CH_3), 6.49 (d, 1H, J = 8.7 Hz, 5- CH), 6.65 (s, 1H, 9- CH), 7.28 (d, 1H, J = 8.8 Hz, 6- CH).

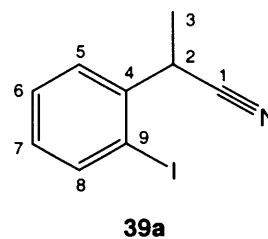


(-)-2-(2-Iodophenyl)propionitrile^[4] **39a**

Synthesis according to GP5 from commercially available (2-iodophenyl)acetonitrile **38** (8.21 g, 33.8 mmol) and methyl iodide (7.19g, 50.65 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 97% (8.43 g, 32.8 mmol), yellow oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.60 (d, 3H, J = 7.1 Hz, 3- CH_3), 4.24 (q, 1H, J = 7.5 Hz, 2- CH), 7.03 (td, 1H, J = 7.6, 1.5 Hz, 7- CH), 7.42 (td, 1H, J = 7.5, 1.1 Hz, 6- CH), 7.61 (dd, 1H, J = 7.6, 1.7 Hz, 5- CH), 7.85 (dd, 1H, J = 8.0, 1.5 Hz, 8- CH).



^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 21.0 (1-C), 36.6 (2-C), 98.8 (9-C), 121.6 (1-C), 123.5, 128.0, 129.7, 130.2, 140.4 (4-C).

$[\alpha]_{\text{D}}^{21.9} = -31.2$ ($c = 2.33$, CHCl_3)

IR (neat): ν (cm^{-1}) = 2938.4 (s), 2925.2 (s), 2840.4 (s), 2352.5 (w), 2235.7 (w), 1730.7 (m), 1465.5 (s), 1433.7 (m), 1375.3 (w), 1269.2 (w), 1083.6 (w), 1009.3 (s), 754.7 (s).

LR: m/z (EI) = 256.9 (100), 241.9 (38.7), 127.9 (53.1), 103.1 (32.1).

HR: m/z (EI) = measured: 256.9690, $\text{C}_9\text{H}_8\text{N}_1\text{I}$ calculated: 256.9702

HPLC Separation: preparative Chiracel OD column, 98:1 hexane:2-propanol, 3 mL/min, 10 $^{\circ}\text{C}$, $t_{\text{R}} = 50.9$ min (–)-enantiomer, 54.5 min (+)-enantiomer.

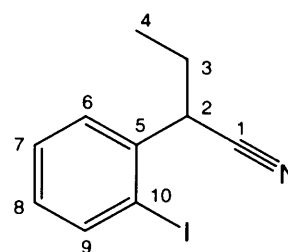
(±)-2-(2-iodophenyl)butyronitrile^[4] **39b**

Synthesis according to GP5 from commercially available (2-iodophenyl)acetonitrile **38** (0.864 mmol, 210 mg, 1 eq) and ethyl iodide (1.47 mmol, 229.6 mg, 1.7 eq). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 19% (44.5 mg, 0.16 mmol), yellow oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.15 (t, 3H, $J = 7.5$ Hz, 4- CH_3), 1.88 (m, 2H, 3- CH_2), 4.11 (dd, 1H, $J = 9.0, 5.1$ Hz, 2- CH), 7.02 (td, 1H, $J = 7.5, 1.5$ Hz, 8- CH), 7.40 (td, 1H, $J = 7.6, 1.6$ Hz, 7- CH), 7.55 (dd, 1H, $J = 7.6, 1.5$ Hz, 6- CH), 7.85 (dd, 1H, $J = 8.1, 1.5$ Hz, 9- CH).

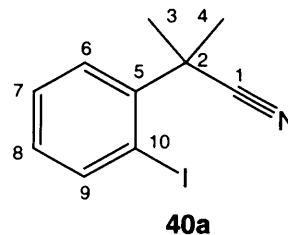
^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 11.8 (4-C), 28.6 (3-C), 40.8 (2-C), 99.2 (10-C), 120.8 (1-C), 128.3, 129.4, 130.1, 140.4 (5-C).



39b

(2-Iodophenyl)-2-methylpropionitrile^[4] 40a

Synthesis according to GP5 from 2-(2-iodophenyl)-2-methylacetonitrile **39a** (1.2 g, 5.13 mmol, 1 eq) and methyl iodide (874.2 mg, 6.16 mmol, 1.2 eq). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1). After work-up and solvent evaporation under reduced pressure, the procedure was repeated.



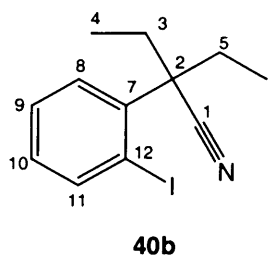
Yield: 71% (973.2 mg, 3.6 mmol), yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 1.84 (s, 6H, 3,4-CH₃), 6.88–6.95 (m, 1H, 8-CH), 7.27–7.40 (m, 2H, 6,7-CH), 7.96 (dd, 1H, *J* = 6.5, 1.3 Hz, 9-CH).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 28.2 (3,4-C), 55.3 (2-C), 96.2 (10-C), 123.5 (1-C), 126.9, 128.8, 129.9, 143.4 (5-C).

1-Ethyl-(2-iodophenyl)butyronitrile^[4] 40b

According to GP5, in a dry flask freshly distilled diisopropylamine (1.54 mmol, 156.2 mg, 1.5 eq) was diluted in dry THF (0.9 mL) and *n*BuLi (0.6 mL, 2.5 M solution in hexane, 1.48 eq) was added at 0 °C and stirred for 10 min. This LDA then was cooled to –78 °C and a solution of **38** (1.029 mmol, 250 mg, 1 eq) in dry THF (1.0 mL) was added dropwise and stirred for 20 min. In following ethyl iodide (1.24 mmol, 192.6 mg, 1.2 eq) was added and this mixture was stirred at room temperature for 3 hours. The dark brown mixture was poured in aqueous saturated NH₄Cl and extracted with EtOAc (5 x 5 mL) and the combined organic phases dried over MgSO₄ and concentrated under reduced pressure after filtration. This crude monosubstituted product again was treated as described above and was then purified by column chromatography (petrol ether/diethyl ether 4/1 (v)).



Yield: 55% (253.3 mg, 0.847 mmol), yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 0.91 (t, 6H, *J* = 7.5 Hz, 4,6-CH₃), 1.94–2.09 (m, 2H, 3- or 5-CH₂), 2.64–2.79 (m, 2H, 5- or 3-CH₂), 6.97 (td, 1H, *J* = 7.5, 1.5 Hz, aromatic), 7.32–7.40 (m, 2H, aromatic), 7.65 (dd, 1H, *J* = 8.0, 1.5 Hz, aromatic), 8.00 (dd, 1H, *J* = 8.0, 1.5 Hz, 11-CH).

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 10.1 (4,6-C), 30.2 (3,5-C), 34.1 (2-C), 92.5 (C-I), 122.8 (1-C), 126.4, 128.5, 129.0, 129.7, 144.1 (7-C).

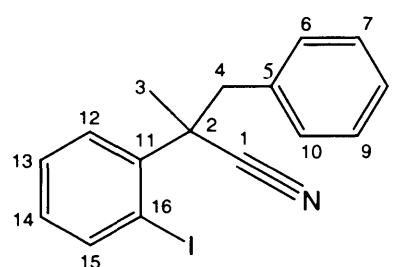
IR (neat): ν (cm^{-1}) = 3062.8 (w) (H_2O), 2978.4 (s), 2925.6 (s), 2872.9 (m), 2218.6 (w), 1713.5 (w), 1581.6 (w), 1465.2 (s), 1382.2 (m), 1260.3 (w), 1080.3 (w), 1007.3 (s), 890.3 (w), 755.7 (s), 700.4 (m).

(+)-2-Benzyl-2-(2-iodophenyl)propionitrile **40c**

Synthesis according to GP5 from (2-iodophenyl)-2-methylacetonitrile **39a** (684.9 mg, 2.67 mmol) and benzyl bromide (683.6 mg, 3.99 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 91% (843.4 mg, 2.43 mmol), yellow oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.78 (s, 3H, 3- CH_3), 3.17 (d, 1H, J = 13.6 Hz, 4- CH_A), 3.60 (d, 1H, J = 13.6 Hz, 4- CH_B), 6.84–6.91 (m, 1H, aromatic), 7.02–7.06 (m, 2H, aromatic), 7.10–7.14 (m, 3H, aromatic), 7.15–7.20 (m, 2H, aromatic), 7.97 (d, 1H, J = 7.9 Hz, 15-CH).



40c

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 25.4 (3-C), 43.6 (2-C), 45.2 (4-C), 95.7 (16-C), 122.6, 127.6, 128.4, 128.8, 129.1, 129.9, 130.6, 135.2, 138.9 (5-C), 143.6 (11-C).

IR (neat): ν (cm^{-1}) = 3317.9 (m) (H_2O), 2925.8 (s), 2360.0 (w), 2246.3 (w), 1693.5 (w), 1599.6 (w), 1555.9 (w), 1495.4 (m), 1454.2 (s), 1375.3 (w), 1258.6 (w), 1078.3 (w), 1030.6 (w), 1009.3 (w), 855.5 (m), 823.7 (m), 760.1 (s), 696.4 (s).

$[\alpha]_\text{D}^{21.9} = -4.8$ (c = 0.53, CHCl_3)

LR: m/z (EI) = 365.1 (95.6), 347.0 (2.1), 315.2 (3.8), 254.1 (5.3), 237.1 (100), 222.1 (3.1), 108.0 (6.3).

HR: m/z (EI) = measured: 365.0509, $\text{C}_{16}\text{H}_{18}\text{N}_2\text{I}$ calculated: 365.0509.

HPLC Separation: preparative Chiracel OD column, 99:1 hexane:2-propanol, 3 mL/min, 10 $^\circ\text{C}$, t_R = 75.3 min (–)-enantiomer, 80.9 min (+)-enantiomer.

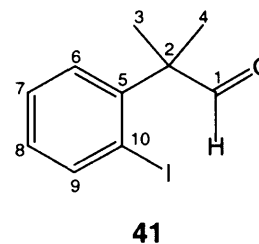
2-(2-Iodophenyl)-2-methylpropionaldehyde^[4] 41

Nitrile **40a** (203.5 mg, 0.751 mmol) was stirred in freshly distilled CH_2Cl_2 (5 mL) in a dry flask under inert atmosphere at 0 °C. DIBAL was added dropwise and the mixture was left to stir for 2 hours. Excess of DIBAL was destroyed by addition of moist SiO_2 . After filtration over Celite, the filtrate was dried over MgSO_4 . The solvent was removed under reduced pressure after filtration.

Yield 8% (16.4 mg, 0.06 mmol), yellow oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.55 (s, 6H, 3,4- CH_3), 6.97–7.02 (m, 1H, 8- CH), 7.41–7.43 (m, 2H, 6,7- CH), 7.94 (dd, 1H, J = 8.0, 0.75 Hz, 9- CH), 9.95 (s, 1H, 1- CH).

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 24.11 (3,4- C), 53.2 (2- C), 98.2 (10- C), 127.2, 128.2, 128.9, 129.6, 143.7 (5- C), 204.3 (1- C).

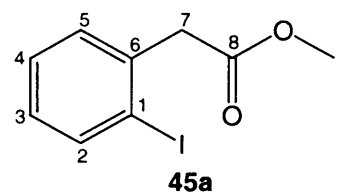
**(2-Iodophenyl)acetic acid methylester^[29] 45a**

Synthesis according to GP4 from commercially available (2-iodophenyl)acetic acid **44** (8.4 g, 32.1 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 91% (8.1 g, 29.2 mmol), yellow oil.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 3.61 (s, 3H, 9- CH_3), 3.71 (s, 2H, 7- CH_2), 6.86 (td, 1H, J = 7.5, 1.8 Hz, 3- CH), 7.36–7.40 (m, 2H, 4-, 5- CH), 7.74 (dd, 1H, J = 7.9, 1.0 Hz, 2- CH).

^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 46.3 (7- C), 52.4 (9- C), 101.2 (1- C), 128.6, 129.1, 130.8, 137.87, 139.67 (6- C), 171.1 (8- C).



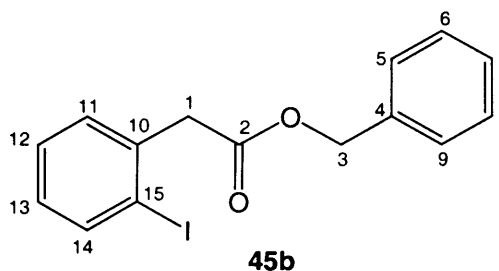
(2-Iodophenyl)acetic acid benzylester 45b

Synthesis according to GP4 from commercially available (2-iodophenyl)acetic acid **44** (4.7 g, 17.93 mmol) and benzylalcohol (2.91 g, 26.89 mmol, 1.5 eq). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 63% (3.96 g, 11.3 mmol), yellow oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 3.85 (s, 2H, 1- CH_2), 5.18 (s, 2H, 3- CH_2), 6.95–6.99 (m, 1H, 11- CH), 7.34–39 (m, 2H, 12,13- CH), 7.85 (d, 1H, $J = 7.9$ Hz, 14- CH).

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 46.6 (1-C), 67.1 (3-C), 101.6 (15-C), 128.1, 128.6, 128.8, 128.8, 128.9, 129.3, 131.0, 138.0 (4-C), 139.8 (10-C), 172.2 (2-C).

**(-)-2-(2-Iodophenyl)acetic acid (3S)-endo-bornylester 45c**

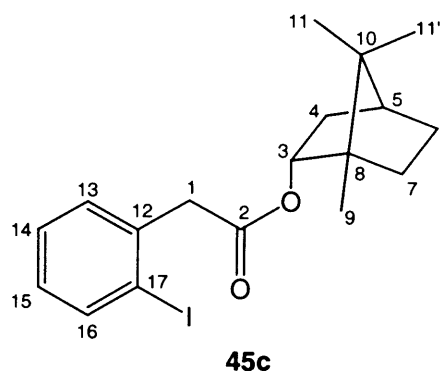
Synthesis according to GP4 from commercially available (2-iodophenyl)acetic acid **44** (1.04 g, 4.0 mmol) and (-)-borneol (0.92 g, 6.0 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 99% (1.6 g, 3.9 mmol), colourless oil.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.79 (s, 3H, 9- CH_3), 0.84 (s, 3H, 11- CH_3), 0.88 (s, 3H, 11'- CH_3), 1.02 (dd, 1H, $J = 13.8, 3.4$ Hz, bornyl), 1.09–1.28 (m, 2H, bornyl), 1.61–1.80 (m, 3H, bornyl), 2.27–2.40 (m, 1H, bornyl), 3.81 (s, 2H, 1- CH_2), 4.84–4.93 (ddd, 1H, $J = 9.9, 5.5, 1.3$ Hz, 3- CH), 6.92–7.00 (m, 1H, aromatic), 7.28–7.35 (m, 2H, aromatic), 7.85 (dd, 1H, $J = 8.5, 0.9$ Hz, 16- CH).

^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 13.9 (9-C), 19.2 (11- or 11'-C), 20.0 (11- or 11'-C), 27.3, 28.3, 37.0, 45.2, 47.1, 48.1, 49.2, 81.1 (3-C), 101.4 (17-C), 128.7, 129.1, 130.9, 138.6, 139.8 (12-C), 171.0 (2-C).

$[\alpha]_{\text{D}}^{25.3} = -24.2$ ($c = 0.53$, CHCl_3)



IR (neat): ν (cm^{-1}) = 3059.2 (w) (H_2O), 2955.8 (s), 2871.1 (m), 1730.4 (s), 1584.7 (w), 1561.2 (w), 1467.1 (m), 1448.3 (m), 1434.2 (m), 1410.7 (w), 1373.1 (w), 1335.5 (m), 1302.6 (w), 1250.9 (s), 1218.0 (s), 1152.2 (s), 1109.9 (m), 1015.8 (s), 818.4 (w), 738.5 (m), 649.1 (w).

LR: m/z (EI) = 417.3 (13.9), 416.0 (100), 290.1 (40.8), 154.0 (15.8), 137.0 (84.1), 121.0 (15.4), 108.0 (44.8), 95.1 (55.3), 81.1 (31.6).

HR: m/z (EI) = measured: 416.1084, $\text{C}_{18}\text{H}_{27}\text{O}_2\text{NI}$ calculated: 416.1081

(-)-2-(2-Iodophenyl)acetic acid (3*R*,5*R*,8*S*)-menthylester **45d**

Synthesis according to GP4 from commercially available (2-iodophenyl)acetic acid **44** (2.92 g, 11.13 mmol) and *L*-menthol (2.61g, 16.7 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 95% (4.24 g, 10.6 mmol), colourless oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 0.73 (d, 3H, J = 6.9

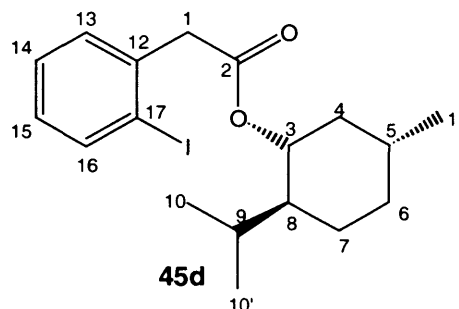
Hz, 11- CH_3), 0.86 (d, 3H, J = 6.9 Hz, 10- CH_3), 0.90 (d, 3H, J = 6.6 Hz, 10'- CH_3), 1.01 (t, 2H, J = 11.9 Hz, menthyl), 1.25–1.42 (m, 2H, menthyl), 1.43–1.53 (m, 1H, menthyl), 1.60–1.74 (m, 2H, menthyl), 1.77–1.91 (m, 1H, menthyl), 1.99–2.10 (m, 1H, menthyl), 3.77 (s, 2H, 1- CH_2), 4.71 (td, 1H, J = 10.9, 4.4 Hz, 3- CH), 6.92–6.99 (m, 1H, aromatic), 7.21–7.36 (m, 2H, aromatic), 7.85 (d, 1H, J = 7.8 Hz, 16- CH).

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 16.8 (11-C), 21.2 (10- or 10'-C), 22.4 (10- or 10'-C), 23.8, 26.6, 31.8, 34.6, 41.1, 47.0, 50.6, 75.3 (3-C), 110.4 (17-C), 128.7, 129.1, 138.4, 139.8 (12-C), 170.9 (2-C).

$[\alpha]_{\text{D}}^{24.3} = -42.1$ (c = 1.17, CHCl_3)

IR (neat): ν (cm^{-1}) = 3375.6 (m) (H_2O), 2929.5 (s), 2860.8 (s), 2346.0 (w), 1729.3 (s), 1585.1 (w), 1562.1 (w), 1451.7 (s), 1370.2 (m), 1247.9 (m), 1218.8 (m), 1166.4 (m), 1096.5 (w), 1038.3 (m), 1020.8 (m), 985.8 (m), 916.0 (w), 846.1 (w), 735.4 (m).

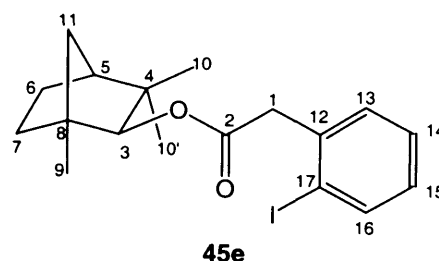
LRMS: m/z (EI) = 418.1 (22.1), 292.2 (62.8), 273.2 (29.2), 156.1 (45.4), 136.1 (70.3), 108.0 (22.0), 91.0 (100), 81.0 (87.5), 58.1 (48.7).



HRMS: m/z (EI) = measured: 418.1241, $C_{18}H_{29}O_2NI$ calculated: 418.1237

(+)-2-(2-Iodophenyl)acetic acid (3*R*)-endo-fenchylester 45e

Synthesis according to GP4 from commercially available (2-iodophenyl)acetic acid **44** (1.01 g, 3.9 mmol) and (1*R*)-endo-(+)-fenchyl alcohol (0.89 g, 5.793 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).



Yield: 60% (0.9 g, 2.3 mmol), colourless oil

1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.72 (s, 3H, 9- CH_3), 0.92–1.03 (m, 1H, fenchyl), 1.02 (s, 3H, 10- CH_3), 1.07 (s, 3H, 10'- CH_3), 1.15 (dd, 1H, J = 10.1, 1.3 Hz, fenchyl), 1.35–1.46 (m, 1H, fenchyl), 1.52–1.62 (m, 3H, fenchyl), 1.68 (d, 1H, J = 3.7 Hz, fenchyl), 3.85 (s, 2H, 1- CH_2), 4.38 (d, 1H, J = 1.9 Hz, 3- CH), 6.91–7.01 (m, 1H, aromatic), 7.29–7.35 (m, 2H, aromatic), 7.84 (d, 1H, J = 7.9 Hz, 16- CH).

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 19.8 (9-C), 20.6, 26.1 (10- or 10'-C), 26.9 (10- or 10'-C), 30.0, 39.9, 41.7, 46.9, 48.6, 48.7, 87.3 (3-C), 101.4 (17-C), 128.7, 129.1, 131.0, 138.5, 139.8 (12-C), 171.2 (2-C).

$[\alpha]_D^{25.3}$ = 13.8 (c = 0.53, $CHCl_3$)

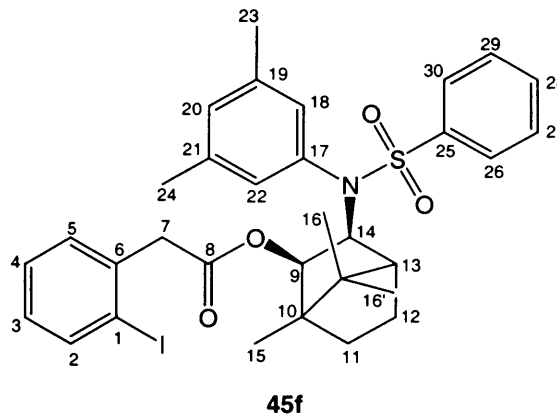
IR (neat): ν (cm^{-1}) = 3423.7 (w) (H_2O), 3057.3 (w), 2857.4 (s), 2868.5 (m), 2357.8 (w), 1729.2 (s), 1584.9 (w), 1562.7 (w), 1468.3 (m), 1435.0 (w), 1407.2 (w), 1368.4 (w), 1335.1 (m), 1251.8 (s), 1212.9 (s), 1157.4 (s), 1101.9 (w), 1035.3 (s), 1007.5 (s), 802.1 (w), 757.7 (w), 730.0 (m).

LRMS: m/z (EI) = 416.2 (14.4), 290.3 (100), 154.2 (30.4), 137.1 (73.5), 106.0 (27.2).

HRMS: m/z (EI) = measured: 416.1080, $C_{18}H_{27}O_2NI$ calculated: 416.1081

(2-Iodophenyl)acetic acid *N*-benzenesulfonamide-*N*-(3,5-dimethylphenyl)-*N*-isobornyl ester **45f**

A mixture of alcohol **57** (110 mg, 0.27 mmol, 1 eq), (2-iodophenyl)acetic acid **44** (202 mg, 0.8 mmol, 3 eq), 1,3-dicyclohexylcarbodiimide (165 mg, 0.81 mmol, 3 eq) and 4-dimethylaminopyridine (98 mg, 81 mmol, 3 eq) in acetonitrile (8 mL) was stirred for 2 d at 60–80 °C. After work-up using aqueous saturated NaHCO₃ (7 mL) and CH₂Cl₂ (4 x 20 mL) and drying over MgSO₄ and



solvent evaporation under reduced pressure, ester **45f** was purified by column chromatography (petrol ether/diethyl ether 4/1) to give a white-greenish solid.

Yield 61% (108.3 mg, 0.5 mmol).

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.57 (s, 3H, 15-CH₃), 0.92–0.97 (m, 1H, cyclohexyl), 0.97 (s, 3H, 16-CH₃), 0.99 (s, 3H, 16'-CH₃), 1.16–1.23 (m, 1H, cyclohexyl), 1.45–1.51 (m, 1H, cyclohexyl), 1.59–1.64 (m, 2H, cyclohexyl), 2.10 (s, 3H, 23-CH₃), 2.28 (s, 3H, 24-CH₃), 3.54 (d, 1H, *J* = 6.2 Hz, 14-CH), 3.76 (d, 1H, *J* = 2.7 Hz, 9-CH), 3.98 (s, 2H, 7-CH₂), 5.84 (s, 1H, 18- or 22-CH), 6.90 (s, 1H, 22- or 18-CH), 6.97 (dt, 1H, *J* = 7.6, 1.6 Hz, 3-CH), 6.99 (s, 1H, 20-CH), 7.24 (dd, 1H, *J* = 7.6, 1.7 Hz, 5-CH), 7.32 (dt, 1H, *J* = 7.4, 1.1 Hz, 4-CH), 7.42–7.46 (m, 2H, 27-, 29-CH), 7.50–7.52 (m, 2H, 26-, 30-CH), 7.60 (tt, 1H, *J* = 7.4, 1.2 Hz, 28-CH), 7.85 (dd, 1H, *J* = 7.9, 1.1 Hz, 2-CH).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 12.2 (15-C), 21.4 (16- or 16'-C), 22.1 (16'- or 16-C), 28.3, 33.5, 47.3, 49.3, 50.2, 54.9, 69.6, 82.9 (9-C), 101.7 (1-C), 128.3, 128.6, 128.8, 129.2, 129.3, 130.1, 131.4, 132.2, 133.4, 135.9, 137.1, 138.3, 139.2, 139.9.

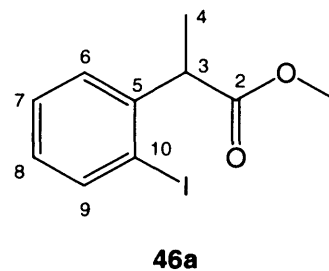
IR (neat): ν (cm⁻¹) = 2354.8, 233.211.

2-(2-Iodophenyl)propionic acid methylester 46a

Synthesis according to GP5 from (2-iodophenyl)acetic acid methylester **45a** (3.51 g, 12.6 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 75% (2.78 g, 9.5 mmol), yellow oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.45 (d, 3H, $J = 7.1$ Hz, 4- CH_3), 3.68 (s, 3H, 1- CH_3), 4.11 (q, 1H, $J = 7.1$ Hz, 3- CH), 6.95 (td, 1H, $J = 7.7, 1.9$ Hz, 8- CH), 7.20 (dd, 1H, $J = 7.8, 1.4$ Hz, 6- CH), 7.31 (td, 1H, $J = 7.5, 0.9$ Hz, 7- CH), 7.85 (dd, 1H, $J = 7.9, 1.1$ Hz, 9- CH).



^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 18.6 (4-C), 49.9 (3-C), 52.5 (1-C), 101.3 (10-C), 127.8, 129.1, 129.1, 140.1, 143.9 (5-C), 174.8 (2-C).

$[\alpha]_{\text{D}}^{25.3} = -70.7^\circ$ ($c = 0.65$, CHCl_3)

IR (neat): ν (cm^{-1}) = 3436.3 (broad band) (H_2O), 2966.2 (w), 2919.2 (w), 2343 (w), 1736.9 (s), 1648.7 (m), 1548.8 (m), 1466.6 (m), 1431.3 (m), 1331.4 (w), 1260.9 (m), 1202.1 (w), 1084.6 (m), 1008.2 (m), 790.8 (m).

LRMS: m/z (EI) = 290.1 (2.2), 231.0 (27.8), 163.1 (99.8), 104.2 (100). 103.1 (69.6), 77.2 (44.3), 59.1 (63.9).

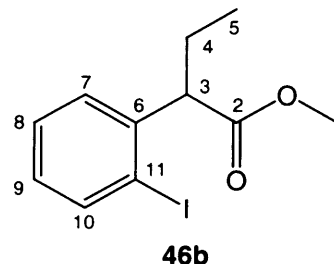
HRMS: m/z (EI) = measured: 308.0142, $\text{C}_{10}\text{H}_{11}\text{O}_2\text{I}^+\text{NH}_4^+$ calculated: 308.0142

HPLC Separation: Chiracel OD-H column, 99:1 hexane:2-propanol, 0.5 mL/min, 10 $^\circ\text{C}$, $t_{\text{R}} = 24.5$ min (–)-enantiomer, 27.5 min (+)-enantiomer.

2-(2-Iodophenyl)butyric acid methylester 46b

Synthesis according to GP5 from (2-iodophenyl)acetic acid methylester **45a** (3.2 g, 11.61 mmol) and ethyl iodide (2.35 mg, 15.1 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 95% (3.34 g, 11.0 mmol), yellow oil.



^1H NMR (400 MHz, CDCl_3): δ (ppm) = 0.91 (t, 3H, $J = 7.4$ Hz, 5- CH_3), 1.65–1.87 (m, 1H, 4- CH_A), 1.91–2.13 (m, 1H, 4- CH_B), 3.65 (s, 3H, 1- CH_3), 3.95 (t, 1H, $J = 7.8$ Hz, 3- CH), 6.83–7.00 (m, 1H, aromatic), 7.19–7.40 (m, 2H, aromatic), 7.91 (d, 1H, $J = 7.9$ Hz, 10- CH).

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 12.4 (5-C), 27.2 (4-C), 52.4 (3-C), 56.7 (1-C), 102.2 (11-C), 128.1, 128.9, 129.1, 140.1, 144.4 (6-C), 177.9 (2-C).

$[\alpha]_{\text{D}}^{25.3} = 58.5$ ($c = 9.42$, CHCl_3)

IR (neat): ν (cm^{-1}) = 3433.1 (broad band) (H_2O), 2936.5 (w), 2349.7 (w), 1729.1 (s), 1463.9 (m), 1430.0 (m), 1345.4 (w), 1305.9 (w), 1260.7 (w), 1198.7 (m), 1164.8 (m), 1006.8 (m), 741.6 (m).

LRMS: m/z (EI) = 322.1 (48.2), 196.2 (100), 194.2 (23.4), 168.1 (63.3), 52.2 (73.6).

HRMS: m/z (EI) = measured: 322.0300, $\text{C}_{11}\text{H}_{13}\text{O}_2\text{I}^+\text{NH}_4^+$ calculated: 322.0298

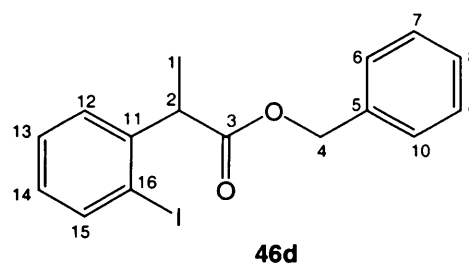
HPLC Separation: Chiracel OD column, 99:1 hexane:2-propanol, 0.5 mL/min, 10 °C, $t_{\text{R}} = 21.6$ min (–)-enantiomer, 24.9 min (+)-enantiomer.

HPLC Separation: preparative Chiracel OD column, 99:1 hexane:2-propanol, 3 mL/min, 10 °C, t_R = 36.2 min (–)-enantiomer, 39.8 min (+)-enantiomer.

(2-Iodophenyl)propionic acid benzylester 46d

Synthesis according to GP5 from **45b** (1280.0 mg, 3.64 mmol, 1eq) and methyl iodide (619.1 mg, 4.36 mmol, 1.2 eq). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 95% (1164.0 mg, 3.46 mmol), yellow oil.



^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.35 (d, 3H, $J = 7.1$ Hz, 1- CH_3), 4.05 (q, 1H, $J = 7.1$ Hz, 2- CH), 5.01 (d, 2H, $J = 4.3$ Hz, 4- CH_2), 6.81 (dt, 1H, $J = 7.9, 1.7$ Hz, 14- CH), 7.09–7.19 (m, 7H, 6,7,8,9,10,12,13- CH), 7.72 (dd, 1H, $J = 7.9, 0.92$ Hz, 15- CH)

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 18.5 (1-C), 49.9 (2-C), 66.8 (4-C), 101.4 (16-C), 110.3, 127.9, 128.3, 128.4, 128.8, 129.0, 129.1, 136.2, 140.0 (5-C), 143.8 (11-C), 174.0 (3-C).

IR (neat): ν (cm^{-1}) = 3062.9 (m), 3020.4 (m), 2967.3 (m), 2876.7 (w), 1732.8 (s), 1578.3 (w), 1557.7 (w), 1495.9 (m), 1462.7 (s), 1452.8 (s), 1436.5 (m), 1371.1 (m), 1327.5 (m), 1327.5 (m), 1245.7 (m), 1202.1 (s), 1169.4 (s), 1082.2 (s), 1005.9 (s), 951.4 (w), 913.3 (w), 744.3 (s), 695.2 (s).

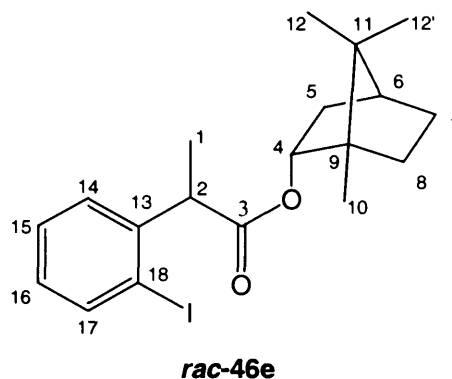
LRMS: m/z (EI) = 366.0 (5), 329.1 (34), 230.9 (99), 216.9 (7), 129.9 (2), 104.0 (97), 91.0 (100).

HRMS: m/z (EI) = measured: 366.0132, $\text{C}_{16}\text{H}_{15}\text{O}_2\text{I}^+\text{NH}_4^+$ calculated 366.0117.

2-(2-Iodophenyl)propionic acid (4S)-(-)-endo-bornylester *rac*-46e

Firstly, some data of the racemic mixture of **46e** are given.

IR (neat): ν (cm⁻¹) = 2930.0 (m), 2852.3 (w), 2354.0 (w), 1702.2 (m), 1594.1 (m), 1448.3 (m), 1359.0 (m), 1218.0 (m), 1195.1 (s), 1181.0 (s), 1120.0 (w), 1099.1 (w), 1067.5 (w), 1015.8 (m), 968.8 (w), 921.8 (m), 813.7 (m), 757.3 (m), 696.2 (m), 668.0 (m).



LRMS: m/z (EI) = 430.2 (34), 318.2 (35), 304.2 (53), 137.0 (100).

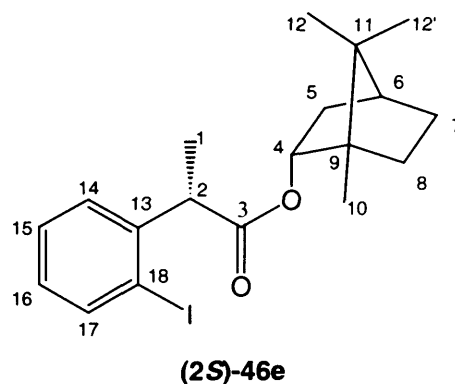
HRMS: calcd. for C₁₉H₂₅IO₂ • NH₄⁺ 430.1237, found 430.1241.

(2S)-2-(2-Iodophenyl)propionic acid (4S)-(-)-endo-bornylester (2S)-46e

Synthesis according to GP5 from **45c** (649.0 mg, 1.63 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 41% (276 mg, 0.67 mmol), colourless oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.82 (s, 3H, 12-CH₃), 0.83 (s, 3H, 12'-CH₃), 0.87 (s, 3H, 10-CH₃), 0.95–1.01 (m, 1H, J = 3.4, 13.7 Hz, bornyl), 1.16–1.22 (m, 2H, bornyl), 1.49 (d, 3H, J = 7.2 Hz, 1-CH₃), 1.59–1.66 (m, 2H, bornyl), 1.70–0.76 (m, 1H, bornyl), 2.28–2.39 (m, 1H, bornyl), 4.13 (q, 1H, J = 7.2 Hz, 2-CH), 4.82–4.86 (ddd, 1H, J = 9.8, 5.6, 1.0 Hz, 4-CH), 6.90–6.93 (m, 1H, aromatic), 7.27–7.33 (m, 2H, aromatic), 7.86 (dd, 1H, J = 7.8, 1.3 Hz, 17-CH).



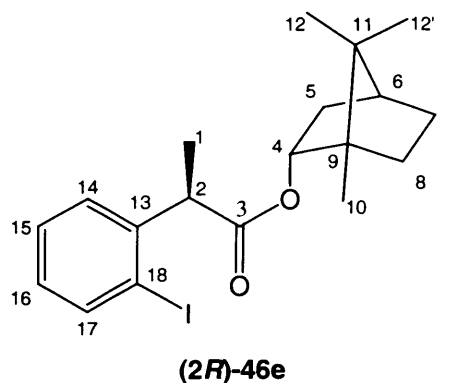
¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 13.5 (1-C), 17.9 (10-C), 18.9 (12- or 12'-C), 19.7 (11'- or 11-C), 27.2, 27.9, 36.6, 44.9, 47.8, 48.9, 49.7, 80.6 (4-C), 102.1 (18-C), 127.6, 128.7, 128.9, 139.7, 143.9 (13-C), 174.1 (3-C).

$[\alpha]_D^{25.6} = 16.5$ (c = 0.66, CHCl₃)

HPLC Separation: preparative Chiracel OD column, 98:1 hexane:2-propanol, 3 mL/min, 10 °C, t_R = 24.9 min.

(2*R*)-2-(2-Iodophenyl)propionic acid (4*S*)-(-)-*endo*-bornylester (2*R*)-46e

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.86 (dd, J = 7.9, 1.2 Hz, 1H, 17-CH), 7.33–7.27 (m, 2H, aromatic), 6.95–6.92 (m, 1H, aromatic), 4.86 (ddd, J = 9.9, 5.5, 1.2 Hz, 1H, 4-CH), 4.14 (q, J = 7.2 Hz, 1H, 2-CH), 2.36–2.25 (m, 1H, bornyl), 1.69–1.64 (m, 2H, bornyl), 1.49 (d, J = 7.2 Hz, 3H, 1-CH₃), 1.21–1.10 (m, 2H, bornyl), 1.01 (dd, J = 13.7, 3.4 Hz, 1H, bornyl), 0.86 (s, 3H, 12'-CH₃), 0.81 (s, 3H, 12-CH₃), 0.83–0.80 (m, 1H, bornyl), 0.63 (s, 3H, 10-CH₃) ppm.



^{13}C NMR (62.5 MHz, CDCl_3): δ (ppm) = 174.1 (3-C), 143.9 (13-C), 139.7, 128.9, 128.7, 127.6, 101.5 (18-C), 80.6 (4-C), 49.8, 48.9, 47.8, 44.9, 36.6, 28.0, 27.1, 19.7 (12'- or 12-C), 18.9 (12- or 12'-C), 17.9 (1-C), 13.5 (10-C).

$[\alpha]_D^{25.4} = -24.1$ (c = 2.26, CHCl_3).

HPLC conditions: preparative Chiracel OD column, 98:1 hexane:2-propanol, 3 mL/min, 10 °C, t_R = 29.0 min.

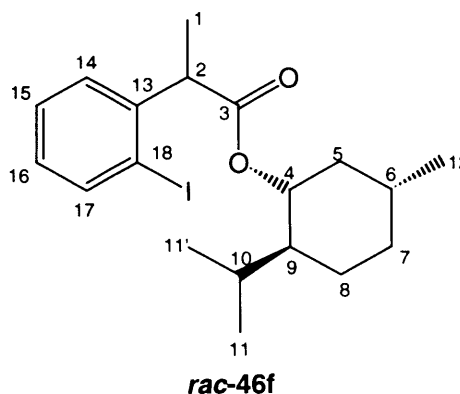
2-(2-Iodophenyl)propionic acid (4*R*,6*R*,9*S*)-menthylester *rac*-46f

Firstly, some data of the racemic mixture of **46f** are given.

IR (neat): ν (cm^{-1}) = 2952.3 (m), 2919.9 (s), 2848.7 (m), 2356.2 (w), 1727.8 (s), 1462.2 (m), 1371.5 (w), 1258.1 (m), 1203.0 (w), 1173.8 (m), 1086.4 (m).

LRMS: m/z (EI) = 432.3 (4), 307.4 (18), 306.3 (100), 287.2 (74), 105.1 (10).

HRMS: calcd. for $\text{C}_{19}\text{H}_{27}\text{IO}_2 \cdot \text{NH}_4^+$ 432.1394, found 432.1393.



(2S)-2-(2-Iodophenyl)propionic acid (4R,6R,9S)-menthylester (2S)-46f

Synthesis according to GP5 from **45d** (317.6 mg, 0.793 mmol) and methyl iodide (146.5 mg, 1.03 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 90% (297 mg, 0.71 mmol), colourless oil.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.76 (d, 3H, J = 6.8 Hz, 12- CH_3), 0.79–0.88 (m, 2H, menthyl) 0.86 (d, 3H, J = 7.8 Hz, 11- CH_3), 0.88 (d, 3H, J = 8.3 Hz, 11'- CH_3), 0.92–1.04 (m, 2H, menthyl), 1.24–1.35 (m, 1H, menthyl), 1.47 (d, 3H, J = 6.4 Hz, 1- CH_3), 1.56–1.69 (m, 2H, menthyl), 1.83–1.88 (m, 1H, menthyl), 1.88–1.94 (m, 1H, menthyl), 4.12 (q, 1H, J = 7.2 Hz, 2- CH), 4.68 (td, 1H, J = 10.9, 4.4 Hz, 4- CH), 6.95–6.95 (m, 1H, 16- CH), 7.27–7.34 (m, 2H, 14-,15- CH), 7.85 (dd, 1H, J = 7.9, 1.2 Hz, 17- CH).

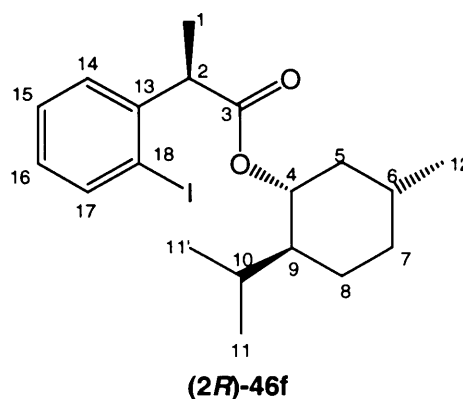
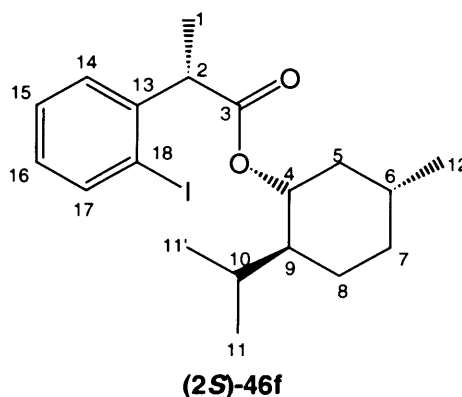
^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 16.4 (1-C), 18.2 (12-C), 20.9 (11- or 11'-C), 22.4 (11'- or 11-C), 23.6, 26.1, 31.7, 34.6, 41.1, 47.3, 50.1, 75.2 (4-C), 101.6 (18-C), 127.8, 128.8, 129.0, 139.9, 144.1 (13-C), 173.9 (3-C).

$[\alpha]_{\text{D}}^{23.0} = -20.9$ (c = 3.04, CHCl_3)

HPLC Separation: preparative Chiracel OD column, 98:1 hexane:2-propanol, 3 mL/min, 10 °C, t_{R} = 19.5 min.

(2R)-2-(2-Iodophenyl)propionic acid (4R,6R,9S)-menthylester (2R)-46f

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.85 (dd, 1H, J = 7.6, 0.9 Hz, 17- CH), 7.32–7.27 (m, 2H, 14-, 15- CH), 6.94–6.91 (m, 1H, 16- CH), 4.61 (td, 1H, J = 10.9, 4.4 Hz, 4- CH), 4.08 (q, 1H, J = 7.1 Hz, 2- CH), 2.07–2.00 (m, 1H, menthyl), 1.69–1.62 (m, 1H, menthyl), 1.62–1.57 (m, 1H, menthyl), 1.46 (d, 3H, J = 7.2 Hz, 1- CH_3), 1.35–1.24 (m, 2H, menthyl), 1.04–0.92 (m, 2H, menthyl), 0.90 (d, 3H, J = 6.5 Hz, 12- CH_3), 0.88–0.79 (m, 2H, menthyl), 0.71 (d, 3H, J = 7.0 Hz, 11'- CH_3), 0.56 (d, 3H, J = 6.9 Hz, 11- CH_3).



^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 173.9 (3-C), 144.1 (13-C), 139.9, 129.0, 128.8, 127.8, 101.7 (18-C), 75.2 (4-C), 50.1, 47.3, 41.1, 34.6, 31.7, 26.1, 23.6, 22.4 (11'- or 11-C), 20.9 (11- or 11'-C), 18.2 (1-C), 16.4 (12-C).

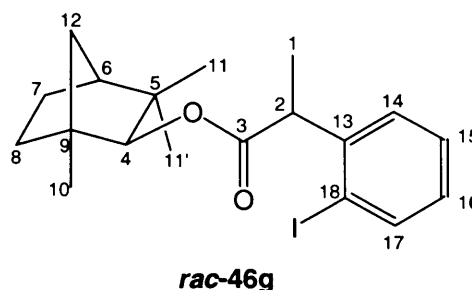
$[\alpha]_{\text{D}}^{24.2} = -73.4$ ($c = 2.53$, CHCl_3).

HPLC conditions: preparative Chiracel OD column, hexane:2-propanol 98:2, 3 mL/min, 10 °C, $t_{\text{R}} = 23.2$ min..

2-(2-Iodophenyl)propionic acid (4*R*)-endo-fenchylester *rac*-46g

Firstly, some data of the racemic mixture of **46g** are given.

IR (neat): ν (cm^{-1}) = 3056.0 (w), 2958.8 (s), 2919.9 (s), 2868.1 (m), 1731.1 (s), 1585.3 (w), 1562.6 (w), 1468.6 (m), 1433.0 (w), 1374.7 (w), 1335.8 (w), 1241.9 (w), 1206.2 (m), 1180.3 (m), 1125.2 (w), 1083.1 (w).



LRMS: m/z (EI) = 431.2 (6.2), 430.2 (32.2), 305.4 (11.5), 304.2 (60.8), 154.0 (56.5), 137.0 (100), 81.1 (27.9).

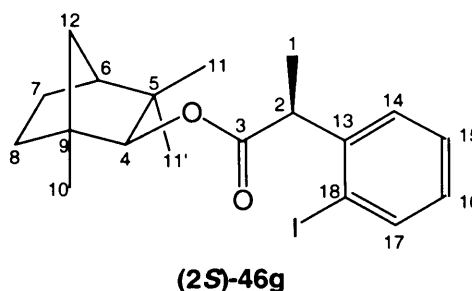
HRMS: m/z (EI) = calcd. for $\text{C}_{19}\text{H}_{25}\text{IO}_2 \bullet \text{NH}_4^+$ 430.1237, found 430.1240.

(2*S*)-2-(2-Iodophenyl)propionic acid (4*R*)-endo-fenchylester (2*S*)-46g

Synthesis according to GP5 from **45e** (542 mg, 1.36 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 89% (497 mg, 1.21 mmol), colourless oil.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.78 (s, 3H, 11- CH_3), 0.90–0.96 (m, 1H, fenchyl), 0.83 (s, 3H, 11'- CH_3), 1.09 (s, 3H, 10- CH_3), 1.13 (dd, 1H, $J = 10.2, 1.4$ Hz, fenchyl), 1.33–1.42 (m, 1H, fenchyl), 1.52 (d, 3H, $J = 7.2$ Hz, 1- CH_3), 1.53–1.55 (m, 1H, fenchyl), 1.56–1.69 (m, 3H,



fenchyl), 4.22 (q, 1H, $J = 7.2$ Hz, 2-CH), 4.35 (d, 1H, $J = 1.9$ Hz, 4-CH), 6.93–6.96 (m, 1H, aromatic), 7.28–7.35 (m, 2H, aromatic), 7.85 (dd, 1H, $J = 7.7, 1.1$ Hz, 17-CH).

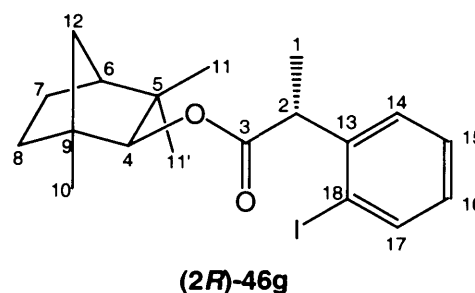
^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 18.2 (10-C), 19.6 (11- or 11'-C), 20.7 (11'- or 11-C), 26.1 (1-C), 26.9, 29.9, 39.7, 41.6, 48.6, 48.7, 50.1, 87.1 (4-C), 101.6 (18-C), 127.9, 128.7, 128.9, 139.9 (13-C), 174.7 (3-C).

$[\alpha]_{\text{D}}^{23.8} = 34.3^\circ$ ($c = 1.43$, CHCl_3)

HPLC Separation: preparative Chiracel OD column, 98:1 hexane:2-propanol, 3 mL/min, 10 $^\circ\text{C}$, $t_{\text{R}} = 22.5$ min.

(2*R*)-2-(2-Iodophenyl)propionic acid (4*R*)-endo-fenchylester (2*R*)-46g

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 7.85 (dd, 1H, $J = 7.7, 1.1$ Hz, 17-CH), 7.35–7.29 (m, 2H, aromatic), 6.95–6.91 (m, 1H, aromatic), 4.33 (d, 1H, $J = 1.9$ Hz, 4-CH), 4.20 (q, 1H, $J = 7.2$ Hz, 2-CH), 1.65–1.62 (m, 2H, fenchyl), 1.62–1.56 (m, 1H, fenchyl), 1.55–1.53 (m, 1H, fenchyl), 1.51 (d, 3H, $J = 7.2$ Hz, 1- CH_3), 1.40–



1.33 (m, 1H, fenchyl), 1.13 (dd, 1H, $J = 10.2, 1.4$ Hz, fenchyl), 1.04 (s, 3H, 11'- CH_3), 1.03 (s, 3H, 11- CH_3), 1.01–0.97 (m, 1H, fenchyl), 0.46 (s, 3H, 10- CH_3).

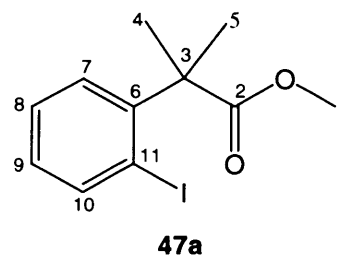
^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 174.5 (2-C), 139.9 (13-C), 129.0, 128.8, 128.1, 127.9, 101.9 (18-C), 87.0 (4-C), 50.1, 48.8, 48.7, 41.6, 39.9, 30.0, 27.0, 26.1, 20.3 (11'- or 11-C), 19.8 (11- or 11'-C), 18.3 (10-C).

$[\alpha]_{\text{D}}^{22.6} = -41.1$ ($c = 0.93$, CHCl_3).

HPLC conditions: preparative Chiracel OD column, hexane:2-propanol 98:2, 3 mL/min, 10 $^\circ\text{C}$, $t_{\text{R}} = 24.5$ min.

2-Methyl-(2-iodophenyl)propionic acid methylester 47a

Synthesis according to GP5 from **45a** (337.7 mg, 1.2 mmol, 1 eq) and methyl iodide (208.4 mg, 1.5 mmol, 1.2 eq). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1). After work-up and solvent evaporation, the procedure was repeated.



Yield: 75 % (273.6 mg, 0.9 mmol), yellow oil.

^1H NMR (250 MHz, CDCl_3): δ (ppm) = 1.63 (s, 6H, 4,5- CH_3), 3.67 (s, 3H, 1- CH_3), 6.79 (td, 1H, J = 7.8, 2.2 Hz, 9-CH), 7.33–7.43 (m, 2H, 7,8-CH), 7.77 (dd, 1H, J = 7.8, 1.2 Hz, 10-CH).

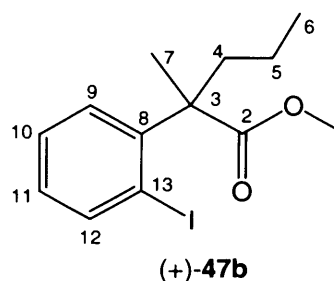
^{13}C NMR (62.5 MHz, CDCl_3): δ (ppm) = 26.6 (4,5-C), 49.4 (3-C), 52.2 (1-C), 98.6 (11-C), 126.3, 127.3, 129.6, 132.9, 145.9 (6-C), 176.3 (2-C).

2-(2-Iodophenyl)-2-propylpropionic acid methylester 47b

Synthesis according to GP5 from **46a** (2.75 g, 9.5 mmol) and 1-propyl iodide (2.1 g, 12.4 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 54% (1.71 g, 5.1 mmol), yellow oil.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.82–0.92 (m, 4H, 5- CH_A and 6- CH_3), 1.15–1.23 (m, 1H, 5- CH_B), 1.62 (s, 3H, 7- CH_3), 1.90–1.98 (m, 1H, 4- CH_A), 2.29–2.35 (m, 1H, 4- CH_B), 3.70 (s, 3H, 1- CH_3), 6.90–6.94 (m, 1H, aromatic), 7.31–7.36 (m, 2H, aromatic), 7.86 (dd, 1H, J = 7.8, 1.1 Hz, 12-CH).



^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 14.9 (6-C), 18.0 (5-C), 25.1 (7-C), 39.6 (4-C), 52.8 (3-C), 53.6 (1-C), 98.6 (13-C), 128.2, 128.4, 128.6, 142.3, 145.5 (8-C), 177.2 (2-C).

$[\alpha]_{\text{D}}^{25.3} = 8.1$ (c = 0.85, CHCl_3)

IR (neat): ν (cm^{-1}) = 3440.4 (broad band) (H_2O), 2933.5 (m), 2854.7 (w), 2347.8 (w), 1729.0, (s), 1644.5 (w), 1458.7 (m), 1430.5 (m), 1374.2 (w), 1301.0 (w), 1233.4 (m), 1132.0 (m), 1075.7 (w), 1008.1 (m), 743.4 (m).

LRMS: m/z (EI) = 350.2 (34.6), 224.2 (62.2), 222.2 (31.5), 182.1 (100), 58.2 (18.5).

HRMS: m/z (EI) = measured: 350.0614, $C_{13}H_{17}O_2I$ NH_4^+ calculated 350.0611

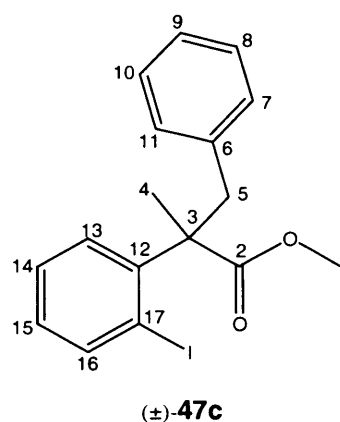
HPLC Separation: preparative Chiracel OD column, 99:1 hexane:2-propanol, 3 mL/min, 10 °C, t_R = 28.1 min (–)-enantiomer, 33.5 min (+)-enantiomer.

2-Benzyl-(2-iodophenyl)propionic acid methylester **47c**

Synthesis according to GP5 from **46a** (2.75 g, 9.5 mmol) and 1-benzyl bromide (2.1 g, 12.4 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield 75% (2.71 g, 7.1 mmol), yellow oil.

1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.55 (s, 3H, 4- CH_3), 3.23 (d, 1H, J = 13.6 Hz, 5- CH_AH), 3.74 (s, 3H, 1- CH_3), 3.87 (d, 1H, J = 13.5 Hz, 5- CH_BH), 6.62–6.64 (m, 2H, aromatic), 6.83 (dd, 1H, J = 7.9, 1.5 Hz, aromatic), 6.92 (td, 1H, J = 7.7, 1.6 Hz, aromatic), 7.04–7.12 (m, 3H, aromatic), 7.16 (dt, 1H, J = 7.8, 1.4 Hz, 14- or 15- CH), 7.99 (dd, 1H, J = 7.8, 1.3 Hz, 16- CH).



^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.7 (4-C), 41.9 (3-C), 53.1 (5-C), 54.2 (1-C), 99.1 (17-C), 126.6, 127.8, 128.0, 128.9, 129.6, 131.1, 136.9, 142.0 (6-C), 143.9 (12-C), 177.3 (2-C).

IR (neat): ν (cm^{-1}) = 3447.9 (w), 2948.9 (s), 2864.0 (m), 1954.3 (w), 1800.4 (w), 1726.0 (s), 1641.1 (m), 1598.7 (m), 1577.4 (m), 1556.2 (w), 1492.5 (s), 1460.7 (s), 1428.8 (s), 1370.4 (s), 1317.3 (m), 1232.4 (s), 1115.6 (s), 1094.4 (s), 1052.0 (m), 1030.7 (m), 1004.2 (s), 983.0 (m), 940.5 (w), 903.3 (m), 860.9 (m), 813.1 (m), 744.1 (s), 712.3 (s), 696.3 (s), 675.8 (m), 637.9 (m), 595.5 (s), 563.6 (m).

LRMS: m/z = 380.0 (2.8), 254.1 (17.6), 253.1 (100), 228.9 (19.8), 193.1 (99.6), 162.1 (77.8), 103.1 (35.8), 91.1 (81.7).

HRMS: m/z = 380.0273 (calculated), $C_{17}H_{17}O_2I$ 380.0270

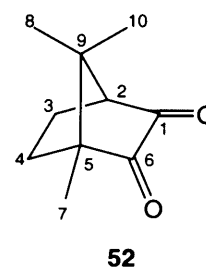
(1*R*)-(+)-Camphorquinone^[30] 52

(1*R*)-(+)-Camphor **51** (3.06 g, 20.1 mmol, 1eq) was heated to 140–150 °C together with SeO₂ (3.7 g, 33.2 mmol, 1.65 eq) and acetic anhydride (3.1 mL) for 3–4 hours. The cooled reaction mixture was filtered and the black selenium waste washed with acetic anhydride. The intensive yellow filtrate was neutralised using aqueous saturated KOH solution and left over night. Yellow crystals were filtered and washed with a petrol ether/hexane solution (5/4) and again recrystallised for further purification.

Yield: 72% (2.4 g, 14.4 mmol).

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.93 (s, 3H, 8-CH₃), 1.06 (s, 3H, 10-CH₃), 1.11 (s, 3H, 7-CH₃), 1.60–1.67 (m, 2H, 4-CH₂), 1.87–1.94 (m, 1H, 3-CH_{ax}), 2.13–2.19 (m, 1H, 3-CH_{eq}), 2.64 (d, 1H, *J* = 5.4 Hz, 2-CH).¹

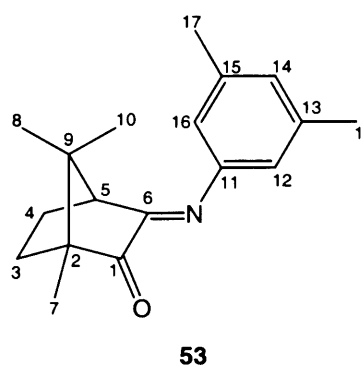
¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 9.12 (7-C), 17.8 (8- or 10-C), 21.5 (10- or 8-C), 22.6 (3-C), 30.3 (4-C), 42.9 (9-C), 58.3 (2-C), 59.0 (5-C), 203.2 (1-C), 205.1 (6-C).¹

***N*-[(3,5-Dimethylphenyl)imino]-*N*-[(1*S*,2*R*,3*S*,4*R*)-4,7,7-trimethylbicyclo[2.2.1]hept-2-one]^[30] 53**

Camphorquinone **52** (1.77g, 10.67 mmol, 1eq) was stirred together with commercially available 3,5-dimethylaniline (1.55 g, 12.8 mmol, 1.2 eq) and anhydrous Na₂SO₄ () at 90–100 °C for 5 hours. The yellow reaction mixture was allowed to cool to r.t., extracted with CH₂Cl₂ (5 x 8 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure after filtration.

Yield 87% (2.5 g, 9.3 mmol).

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.90 (s, 3H, 8-CH₃), 0.98 (s, 3H, 10-CH₃), 1.10 (s, 3H, 7-CH₃), 1.57–1.72 (m, 2H, 4-CH₂), 1.78–1.91 (m, 1H, 3-CH_{ax}), 2.03–2.15 (m, 1H, 3-CH_{eq}), 2.31 (d, 6H, *J* = 0.55 Hz, 17,18-CH₃), 2.82(d, 1H, *J* = 4.7 Hz, 5-CH), 6.52 (s, 2H, 12,16-CH), 6.81 (s, 1H, 14-CH).



¹ Peaks were assigned using SDBS.

IR (neat): ν (cm^{-1}) = 3478.5 (w) (H_2O), 3364.2 (w), 2869.8 (s), 2872.3 (s), 2735.0 (w), 1749.8 (s), 1669.7 (m), 1599.1 (s), 1589.6 (s), 1469.5 (s), 1446.6 (s), 1380.5 (m), 1372.3 (m), 1326.5 (m), 1297.9 (m), 1246.4 (w), 1160.6 (m), 1103.4 (m), 1035.4 (m), 1029.1 (m), 1020.4 (m), 971.9 (m), 926.1 (w), 846.0 (s), 743.1 (w), 691.6 (m), 663.0 (w).

LRMS: m/z (EI) = 269.2 (2), 241.1 (9), 226.1 (2), 213.1 (3), 198.0 (1), 172.0 (12), 158.0 (100), 121.0 (2), 115.9 (3), 105.0 (12), 95.0 (8), 91.0 (2), 77.0 (7), 67.0 (4).

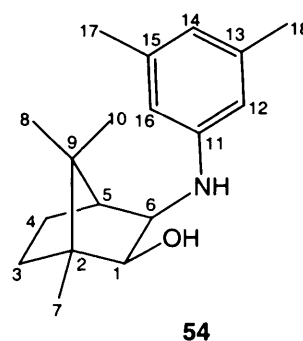
HRMS: m/z (EI) = measured: 269.1775, $\text{C}_{18}\text{H}_{32}\text{O}_1\text{N}_1$ calculated: 269.1774.

N*-[(3,5-Dimethylphenyl)amino]-*N*-[(1*S*,2*R*,3*S*,4*R*)-4,7,7-trimethylbicyclo[2.2.1]hept-2-ol]^[30] **54*

Imine **53** (85.6 mg, 0.32 mmol, 1 eq) was stirred together with NaBH_4 (12 mg, 0.32 mmol, 1 eq) at room temperature in ethanol (5 mL) for 2 hours. The reaction mixture was quenched with 2 M HCl, extracted with CH_2Cl_2 (5 x 7 mL) and dried over Na_2SO_4 . After filtration, the solvent was removed under reduced pressure.

Yield: 66% (57.3 mg, 0.21 mmol).

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.82 (s, 3H, 8- CH_3), 0.99 (s, 3H, 10- CH_3), 1.04–1.14 (m, 2H, camphor), 1.29 (s, 3H, 7- CH_3), 1.42–1.55 (m, 1H, camphor), 1.64–1.72 (m, 1H, camphor), 1.76–1.77 (m, 1H, camphor), 2.29 (s, 6H, 17,18- CH_3), 3.47 (d, 1H, $J = 7.2$ Hz, 6- CH), 4.01 (d, 1H, $J = 7.2$ Hz, 1- CH), 6.82 (s, 3H, 12,14,16- CH).

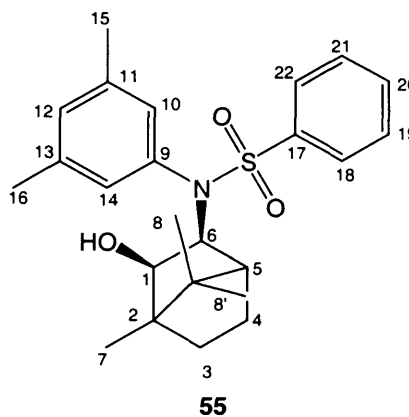


LRMS: m/z (EI) = 274.2 (100), 74.1 (3), 60.2 (16).

HRMS: m/z (EI) = measured: 274.2168, $\text{C}_{18}\text{H}_{32}\text{O}_1\text{N}_1$ calculated: 274.2165.

N*-(3,5-Dimethylphenyl)-*N*-[(1*S*,2*R*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]benzenesulfonamide^[30] **55*

A mixture of alcohol **54** (2.00 g, 7.3 mmol, 1 eq), benzenesulfonic acid chloride (3.90 g, 21.9 mmol, 3 eq), pyridine (1.73 g, 2.1 mmol, 3 eq) in acetonitrile was stirred for 3 d at room temperature. The reaction mixture was quenched in aqueous saturated NaHCO₃, then extracted with CH₂Cl₂ (3 x 20 mL), dried over MgSO₄ to give a white powder after evaporation of solvents under reduced pressure. Yield 65% (1.96 g, 4.7 mmol).



¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.57 (s, 3H, 7-CH₃), 0.92–0.97 (m, 1H, cyclohexyl), 0.97 (s, 3H, 8-CH₃), 0.99 (s, 3H, 8'-CH₃), 1.17–1.22 (m, 1H, cyclohexyl), 1.45–1.51 (m, 1H, cyclohexyl), 1.58–1.64 (m, 2H, cyclohexyl), 2.10 (s, 3H, 15-CH₃), 2.28 (s, 3H, 16-CH₃), 3.54 (d, 1H, *J* = 6.2 Hz, 6-CH), 3.97 (d, 1H, *J* = 6.2 Hz, 1-CH), 5.83 (s, 1H, 10- or 14-CH), 6.90 (s, 1H, 14- or 10-CH), 6.98 (s, 1H, 12-CH), 7.43–7.46 (m, 2H, 19-CH, 21-CH), 7.50–7.51 (m, 2H, 18-CH, 22-CH), 7.60 (tt, 1H, *J* = 7.3, 1.1 Hz, 20-CH).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 12.2 (7-C), 21.4 (8- or 8'-C), 22.1 (8'- or 8-C), 28.3, 33.5, 47.3, 49.3, 50.2, 69.6, 82.9 (1-C), 128.6, 129.3, 130.1, 132.1, 133.4, 135.9, 139.2, 140.0.

LRMS: *m/z* (EI) = 414.2 (68.9), 274.3 (100), 160.0 (22.9), 122.1 (28.4).

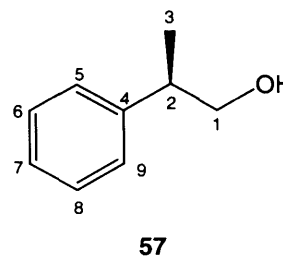
HRMS: *m/z* (EI) = measured: 414.2100, C₂₄H₃₂O₃N₁S₁ calculated: 414.2097.

(*R*)-2-Phenylpropanol **57^[31]**

Synthesis according to GP28 from (2*R*)-**46f** (39 mg, 0.097 mmol) and LiAlH₄ (10.9 mg, 0.288 mmol, 3 eq). Purification by preparative TLC (petrol ether:diethyl ether 2:1), colourless oil.

Yield: 97% (39 mg, 0.094 mmol)

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 1.21 (d, 3H, *J* = 7.0 Hz, 3-CH₃), 1.37 (broad s, 1H, 1-OH), 2.85–2.92 (m, 1H, 2-CH), 3.64 (d, 2H, *J* = 6.8 Hz, 1-CH₂), 7.17–7.19 (m, 3H, aromatic), 7.25–7.28 (m, 2H, aromatic).



$[\alpha]_{\text{D}}^{23.8} = 1.13$ ($c = 3.2$, CHCl_3), Lit: $[\alpha]_{\text{D}}^{25} = 0.76$ (neat).^[32]

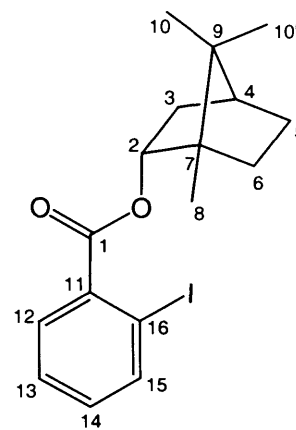
HPLC: Chiracell AD-column, 70% hexane/2-propanol: 8.99 min (commercial compound: 9.0 min).

(–)-2-Iodobenzoic acid (2*S*)-endo-bornylester (–)-60a

Synthesis according to GP4 from commercially available 2-iodobenzoyl chloride **59** (138.2 mg, 0.896 mmol) and (–)-borneol (358.2 mg, 1.344 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 94% (324.0 mg, 0.84 mmol), colourless oil.

¹H NMR (500 MHz, CDCl_3): δ (ppm) = 0.91 (s, 3H, 10- CH_3), 0.94 (s, 3H, 8- CH_3), 0.96 (s, 3H, 10'- CH_3), 1.19 (dd, 1H, $J = 13.9, 3.5$ Hz, bornyl), 1.27–1.41 (m, 2H, bornyl), 1.74 (t, 1H, $J = 4.6$ Hz, bornyl), 1.77–1.83 (m, 1H, bornyl), 2.07–2.13 (m, 1H, bornyl), 2.47–2.53 (m, 1H, bornyl), 5.14 (ddd 1H, $J = 9.9, 5.7, 1.3$ Hz, 2-CH), 7.13–7.17 (m, 1H, 14-CH), 7.41 (td, 1H, $J = 7.6, 1.2$ Hz, 13-CH), 7.79 (dd, 1H, $J = 7.8, 1.7$ Hz, 12-CH), 7.99 (dd, 1H, $J = 7.9, 1.1$ Hz, 15-CH).



60a

¹³C NMR (125 MHz, CDCl_3): δ (ppm) = 14.1 (8-C), 19.3 (10- or 10'-C), 20.1 (10'- or 10-C), 27.8, 28.4, 37.1, 45.3, 48.4, 49.4, 82.2 (2-C), 94.3 (16-C), 128.2, 131.1, 132.7, 141.6 (11-C), 167.3 (1-C).

$[\alpha]_{\text{D}}^{25.8} = -22.0$ ($c = 2.72$, CHCl_3)

IR (neat): ν (cm^{-1}) = 2955.6 (s), 2873.0 (m), 2341.7 (w), 1722.2 (s), 1580.5 (m), 1456.6 (m), 1427.1 (m), 1373.9 (w), 1291.3 (s), 1244.1 (s), 1131.5 (s), 1043.5 (m), 1000.2 (m), 973.0 (w), 737.9 (s).

LRMS: m/z (EI) = 384.1 (12.6), 231.0 (100), 202.9 (30.5), 136.1 (67.9), 109.1 (55.3), 93.1 (47.4), 76.1 (24.5).

HRMS: m/z (EI) = measured: 384.0576, $\text{C}_{17}\text{H}_{21}\text{O}_2\text{I}$ calculated: 384.0581

(-)-2-Iodobenzoic acid (2*R*,4*R*,7*S*)-menthylester (-)-60b

Synthesis according to GP4 from commercially available 2-iodobenzoyl chloride **59** (2.46 g, 9.24 mmol) and *L*-menthol (2.17 g, 13.85 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 98% (3.5 g, 9.1 mmol), colourless oil.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.82 (d, 3H, J = 6.9

Hz, 10- CH_3), 0.92 (d, 3H, J = 7.0 Hz, 9- CH_3), 0.88–0.97 (m,

1H, menthyl), 0.95 (d, 3H, J = 6.9 Hz, 9'- CH_3), 1.07–1.19 (m, 2H, menthyl), 1.51–1.59 (m,

2H, menthyl), 1.69–1.76 (m, 2H, menthyl), 1.96–2.06 (m, 1H, menthyl), 2.15–2.21 (m, 1H,

menthyl), 4.97 (td, 1H, J = 10.9, 4.4 Hz, 2-CH), 7.14 (td, 1H, J = 7.5, 1.7 Hz, 14-C), 7.40 (td,

1H, J = 7.6, 1.2 Hz, 13-C), 7.74 (dd, 1H, J = 7.8, 1.7 Hz, 12-C), 7.98 (dd, 1H, J = 7.9, 1.1 Hz,

15-C).

^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 16.6 (10-C), 21.2 (9- or 9'-C), 22.4 (9'- or 9-C),

23.7, 26.7, 31.9, 34.6, 41.2, 47.5, 76.3 (2-C), 94.2 (16-C), 128.2, 130.8, 132.6, 136.4, 141.5

(11-C), 166.6 (1-C).

$[\alpha]_{\text{D}}^{25.3} = -45.4$ (c = 0.48, CHCl_3)

IR (neat): ν (cm^{-1}) = 2954.5 (s), 2860.5 (m), 2343.4 (w), 1719.2 (s), 1578.2 (w), 1460.7 (w),

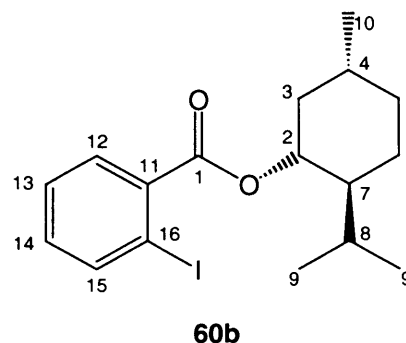
1425.4 (w), 1366.7 (w), 1284.4 (s), 1249.1 (s), 1125.7 (m), 1090.5 (m), 1037.6 (w), 1008.2

(m), 955.3 (w), 737.9 (s).

LRMS: m/z (EI) = 386.1 (100), 380.1 (4.5), 371.2 (3.9), 329.9 (9.6), 321.1 (11.6), 305.0 (3.2),

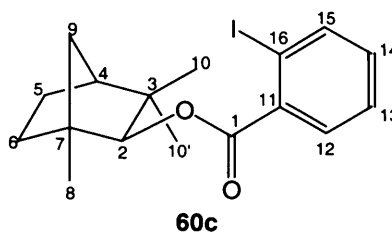
293.1 (3.2), 274.1 (3.0).

HRMS: m/z (EI) = measured: 386.0737, $\text{C}_{17}\text{H}_{23}\text{O}_2\text{I}$ calculated: 386.0737



(+)-2-Iodobenzoic acid (2*R*)-endo-fenchylester (+)-60c

Synthesis according to GP4 from commercially available 2-iodobenzoyl chloride **59** (325 mg, 1.219 mmol) and (1*R*)-endo-(+)-fenchyl alcohol (125.4 mg, 0.813 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).



Yield: 88% (274.3 mg, 1.1 mmol), colourless oil.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.87 (s, 3H, 8- CH_3), 1.14 (s, 3H, 10- CH_3), 1.10–1.18 (m, 1H, fenchyl), 1.20 (s, 3H, 10'- CH_3), 1.23 (dd, 1H, J = 10.4, 1.1 Hz, fenchyl), 1.43–1.53 (m, 1H, fenchyl), 1.63–1.66 (m, 1H, fenchyl), 1.70–1.74 (m, 1H, fenchyl), 1.74–1.76 (m, 1H, fenchyl), 1.84–1.90 (m, 1H, fenchyl), 4.62 (d, 1H, J = 1.9 Hz, 2- CH), 7.14 (td, 1H, J = 7.6, 1.3 Hz, 14- CH), 7.39 (td, 1H, J = 7.6, 0.8 Hz, 13- CH), 7.81 (dd, 1H, J = 7.8, 1.7 Hz, 12- CH), 7.90 (d, 1H, J = 7.9 Hz, 15- CH).

^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 19.9 (10- or 10'-C), 20.7 (10'- or 10-C), 26.1 (8-C), 27.1, 30.0, 40.1, 41.8, 48.7, 48.8, 88.0 (2-C), 94.4 (16-C), 128.1, 130.9, 132.6, 135.9, 141.6 (11-C), 167.1 (1-C).

$[\alpha]_{\text{D}}^{25.9} = 16.2$ (c = 2.46, CHCl_3)

IR (neat): ν (cm^{-1}) = 3412.8 (m) (H_2O), 2935.4 (m), 2868.8(m), 2358 (w), 1712.7 (s), 1579.5 (w), 1462.9 (m), 1368.5 (w), 1290.8 (s), 1268.6 (s), 1135.3 (m), 1107.6 (m), 1029.9 (w), 985.5 (w), 780.0 (m), 741.2 (s), 641.3 (w).

LRMS: m/z (EI) = 384.1 (6.3), 231.0 (100), 202.9 (31.3), 153.1 (37.1), 136.1 (70.3), 81.1 (71.4).

HRMS: m/z (EI) = measured: 384.0578, $\text{C}_{17}\text{H}_{21}\text{O}_2\text{I}$ calculated: 384.0581

(±)-2,2'-Di(2-iodobenzoic acid)-1,1'-binaphthyl ester (±)-65

According to GP4, in a one-necked flask 2-iodobenzoyl chloride **59** (2.7 mmol, 719.5 mg, 3 eq) and *rac*-BINOL **64** (0.9 mmol, 258.1 mg) were refluxed in CHCl₃ for 2 hours.

To this greenish slurry aqueous saturated NaHCO₃ was added and the product extracted with CH₂Cl₂ (5 x 8 mL) and dried over Na₂SO₄. After filtration, the solvent was evaporated under reduced pressure.

Yield: 50% (335.8 mg, 0.45 mmol), white crystals.

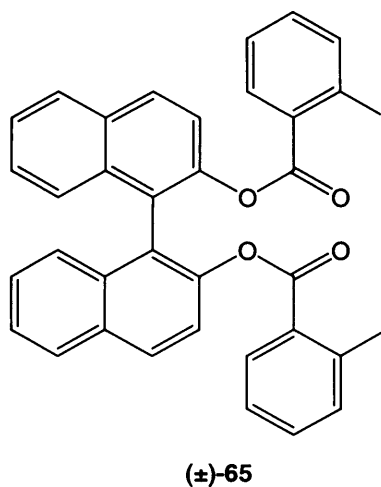
¹H NMR (400 MHz, CDCl₃): δ (ppm) = 6.94 (dd, 2H, *J* = 7.7, 1.6 Hz, aromatic), 6.99 (td, 2H, *J* = 7.5, 1.7 Hz, aromatic), 7.09 (td, 2H, *J* = 7.5, 1.3 Hz, aromatic), 7.34 (m, 2H, aromatic), 7.39 (m, 2H, aromatic), 7.47 (m, 2H, aromatic), 7.62 (d, 2H, *J* = 8.8 Hz, aromatic), 7.84 (dd, 2H, *J* = 7.9, 1.2 Hz, aromatic), 7.95 (d, 2H, *J* = 8.3 Hz, aromatic), 8.8 (d, 2H, *J* = 8.3 Hz, aromatic).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 94.7 (C-I), 122.2, 123.9, 126.3, 126.5, 127.4, 128.1, 128.4, 130.1, 131.3, 132.1, 133.0, 133.7, 134.0, 141.4, 147.1, 164.8 (C=O).

IR (neat): ν (cm⁻¹) = 1745.9 (m), 1579.0 (w), 1508.7 (w), 1463.5 (w), 1428.3 (w), 1237.5 (m), 1202.5 (m), 1080.9 (m), 1036.6 (w), 1012.3 (m), 805.7 (w), 735.3 (m).

LRMS: *m/z* (EI) = 746.1 (3), 344.3 (1), 315.3 (3), 282.3 (7), 268.2 (15), 231.1 (100), 203.1 (46), 180.2 (4), 152.2 (8), 105.2 (62), 77.2 (45), 76.2 (85), 50.3 (38).

HRMS: *m/z* (EI) = measured ([M⁺NH₄]⁺): 763.9796, C₃₄H₂₄O₄N₁I₂ calculated: 763.9789



(S)-(-)-2-Iodobenzoic acid binaphthylamide (S)-(-)-67

Synthesis according to GP6 commercially available 2-iodobenzoyl chloride **59** (307.8 mg, 1.155 mmol) and (S)-(-)-1,1'-binaphthyl-2,2'-diamine **66** (109.5 mg, 0.385 mmol). The product was purified by flash column chromatography (petrol ether:diethyl ether 4:1).

Yield: 92% (263.8 mg, 0.35 mmol), white powder.

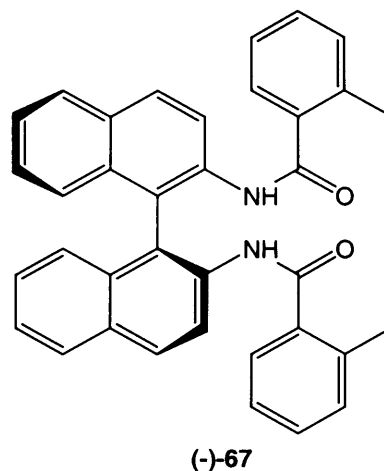
^1H NMR (500 MHz, CDCl_3): δ (ppm) = 6.92 (dd, 2H, J = 7.6, 1.5 Hz, aromatic), 6.97 (td, 2H, J = 7.6, 1.6 Hz, aromatic), 7.15–7.20 (m, 4H, aromatic), 7.30–7.36 (m, 2H, aromatic), 7.46–7.49 (m, 2H, aromatic), 7.70 (d, 2H, J = 7.9 Hz, aromatic), 7.97 (d, 2H, J = 8.2 Hz, aromatic), 8.10 (d, 2H, J = 9.0 Hz, aromatic), 8.56 (d, 2H, J = 8.9 Hz, aromatic).

^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 92.6 (C-I), 110.4, 122.6, 125.7, 125.7, 126.3, 127.9, 128.5, 128.8, 130.5, 131.8, 132.1, 132.9, 135.1, 140.3, 141.5, 168.5 (C=O).

IR (neat): ν (cm^{-1}) = 3455.7 (m) (H_2O), 3078.2 (w), 3021.0 (m), 2860.8 (w), 2357.5 (w), 1949.9 (w), 1875.6 (w), 1818.4 (w), 1668.2 (w), 1595.3 (m), 1490.5 (s), 1451.6 (s), 1383.7 (w), 1332.2 (w), 1297.9 (w), 1158.4 (m), 1073.4 (s), 1029.1 (m), 983.3 (m), 960.7 (s), 908.2 (m), 850.3 (m), 765.2 (s), 693.9 (s), 605.0 (m).

LRMS: m/z (EI) = 744.98 (100), 686.37 (14.5), 680.48 (8.7).

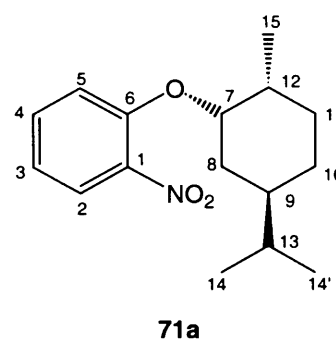
HRMS: m/z (EI) = measured: 744.9877, $\text{C}_{34}\text{H}_{23}\text{O}_2\text{N}_2\text{I}_2$ calculated: 744.9849

**(-)-1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-2-nitrobenzene (-)-71a**

Following GP1, NaH (496.4 mg, 15.9 mmol, 2.2 eq) in THF (10 mL) were stirred with 1-fluoro-2-nitrobenzene **70** (1.02 g, 762 μl , 7.22 mmol, 1 eq) and *L*-menthol (2.48 g, 15.9 mmol, 2.2 eq).

Yield: 94% (1.9 g, 6.86 mmol), yellow oil.

^1H NMR (250 MHz, CDCl_3): δ (ppm) = 0.74 (d, 3H, J = 6.8 Hz, 15- CH_3), 0.91 (d, 3H, J = 6.4 Hz, 14- CH_3), 0.92 (d, 3H, J = 7.2



Hz, 14'-CH₃), 0.95–1.03 (m, 1H, menthyl), 1.04–1.16 (m, 2H, menthyl), 1.43–1.53 (m, 1H, menthyl), 1.57–1.64 (m, 1H, menthyl), 1.69–1.77 (m, 2H, menthyl), 2.09–2.14 (m, 1H, menthyl), 2.17–2.25 (m, 1H, 13-CH), 4.20 (dt, 1H, $J = 10.5, 4.1$ Hz, 7-CH), 6.92–6.99 (m, 1H, 5-CH), 7.08 (d, 1H, $J = 8.3$ Hz, 4-CH), 7.44–7.51 (m, 1H, 3-CH), 7.76 (dd, 1H, $J = 8.1, 1.7$ Hz, 2-CH).

¹³C NMR (62.5 MHz, CDCl₃): δ (ppm) = 16.7 (15-C), 21.1 (14- or 14'-C), 22.4 (14'- or 14-C), 23.8, 26.1, 31.8, 34.6, 40.0, 47.9, 79.6 (7-C), 115.4, 119.9, 125.8, 133.9, 151.9 (6-C).

$[\alpha]_D^{24.5} = -69.9$ ($c = 2.89$, CHCl₃).

IR (neat): ν (cm⁻¹) = 2954.9 (s), 2860.9 (w), 1607.8 (m), 1525.5 (s), 1478.5 (w), 1349.3 (m), 1278.8 (m), 1249.4 (w), 744.0 (w).

LRMS: m/z (EI) = 277.2 (1), 153.1 (7), 139.2 (27), 138.2 (50), 97.2 (16), 83.2 (100), 81.2 (26), 55.1 (37).

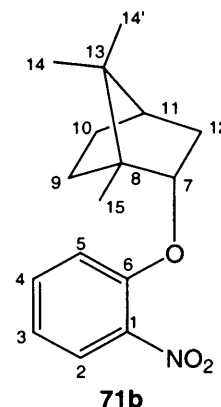
HRMS: m/z (EI) = measured: 277.1672, C₁₆H₂₃NO₃ calculated: 277.1672

(-)- (1R,2S,4S)-1,7,7-Trimethyl-2-(2-nitrophenyl)oxy-bicyclo[2.2.1]heptane (-)-71b

According to GP1 NaH (223.7 mg, 5.59 mmol, 2.2 eq) was stirred with 1-fluoro-2-nitrobenzene **70** (358.4 mg, 2.54 mmol, 1 eq) and (-)-borneol (862.3 mg, 5.59 mmol, 2.2 eq). After purification by flash column chromatography, the product was obtained as a yellow oil in good yields of 90% (630 mg, 2.3 mmol).

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 0.93 (s, 3H, 15-CH₃), 0.95 (s, 6H, 14,14'-CH₃), 1.16 (dd, 1H, $J = 13.4, 3.2$ Hz, borneyl), 1.25–1.41 (m, 2H, borneyl), 1.73–1.82 (m, 2H, borneyl), 2.25–2.32 (m, 1H, borneyl), 2.37–2.44 (m, 1H, borneyl), 4.40–4.45 (m, 1H, 7-CH), 6.92 (d, 1H, $J = 8.7$ Hz, 5-CH), 6.96 (t, 1H, $J = 7.7$ Hz, aromatic), 7.45–7.49 (m, 1H, aromatic), 7.83 (dd, 1H, $J = 8.1, 1.6$ Hz, 2-CH).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 13.6 (15-C), 19.0 (14- or 14'-C), 19.7 (14'- or 14-C), 26.8, 27.8, 36.7, 45.2, 47.6, 49.9, 85.1 (7-C), 115.4, 119.5, 125.6, 133.9, 152.5 (6-C).



$[\alpha]_{\text{D}}^{24.5} = -93.4$ ($c = 1.85$, CHCl_3).

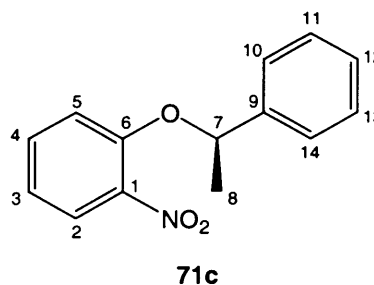
IR (neat): ν (cm^{-1}) = 2946.8 (m), 2872.7 (m), 1608.8 (s), 1577.9 (m), 1522.3 (s), 1355.6 (s), 1281.5 (s), 1164.1 (m), 1114.7 (m), 1022.1 (m), 991.2 (m), 867.7 (m), 830.6 (m), 738.0 (s).

LRMS: m/z (EI) = 275.2 (3), 153.1 (5), 138.2 (10), 137.2 (100), 95.2 (32), 81.2 (71), 69.1 (14), 40.9 (10).

HRMS: m/z (EI) = measured: 275.1518, $\text{C}_{16}\text{H}_{21}\text{O}_3\text{N}$ calculated: 275.1516

(*R*)-1-(2-Nitrophenyl)-1-phenylethylether (*R*)-71c

1-Fluoro-2-nitrobenzene **70** (525.73 mg, 3.72 mmol, 1 eq) and (*R*)-phenylethanol (500 mg, 4.09 mmol, 1.1 eq) were dissolved in dry THF under inert conditions and cooled to 0 °C. To this solution (8.19 mL, 4.09 mmol, 1.1 eq) of potassium-bis(trimethylsilyl)amide (0.5 M in toluene) were added dropwise. The mixture was stirred for 4 hours from 0 °C to rt.



The reaction was quenched with aqueous saturated NH_4Cl , extracted with CH_2Cl_2 (5 x 5 mL) and dried over MgSO_4 . After filtration, evaporation of the solvents afforded 862.2 mg (3.54 mmol, 95%) of the product as a yellow oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.53 (d, 3H, $J = 6.4$ Hz, 8- CH_3), 5.28 (q, 1H, $J = 6.4$ Hz, 7- CH), 6.73–6.82 (m, 2H, aromatic), 7.10–7.25 (m, 6H, aromatic), 7.61 (dd, 1H, $J = 8.1$, 1.7 Hz, 2- CH).

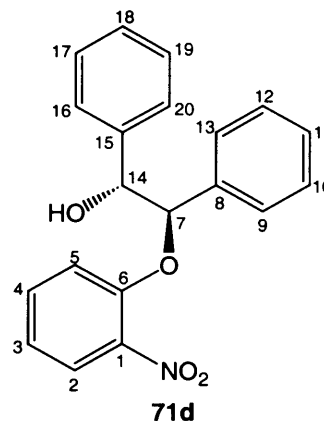
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 21.9 (8-C), 76.1 (7-C), 114.5, 118.4, 123.5, 123.7, 124.8, 125.1, 127.0, 131.7, 140.0 (9-C), 149.3 (6-C).

$[\alpha]_{\text{D}}^{25.1} = -86.2$ ($c = 0.48$, CHCl_3).

IR (neat): ν (cm^{-1}) = 3567.6 (w) (H_2O), 3434.6 (w), 3035.4 (m), 2974.9 (m), 2928.5 (m), 1955.2 (w), 1888.7 (w), 1816.1 (w), 1604.4 (s), 1525.8 (s), 1483.4 (s), 1447.1 (m), 1356.4 (s), 1277.8 (s), 1253.6 (s), 1162.9 (m), 1066.1 (m), 1005.6 (m), 927.0 (m), 848.4 (m), 745.5 (s), 697.2 (s), 666.9 (m), 606.4 (m).

(*R,R*)-1-(2-Nitrophenyl)hydrobenzoinether (*R,R*)-71d

Under inert conditions 35.9 mg (0.26 mmol, 1 eq) of 1-fluoro-2-nitrobenzene **70** and 60 mg (0.28 mmol, 1.1 eq) of (*R,R*)-hydrobenzoin were dissolved in dry THF and cooled to 0 °C. To this solution 0.56 mL (0.28 mmol, 1.1 eq) of potassium-bis(trimethylsilyl)amide (0.5 M in toluene) were added dropwise. The mixture was stirred for 4 hours from 0°C to rt. The reaction was quenched by the addition of aqueous saturated NH_4Cl , extracted with CH_2Cl_2 (5 x 5 mL) and dried over MgSO_4 . After filtration, evaporation of the solvents and preparative TLC (petrol ether:diethyl ether, 4:1) afforded 31.3 mg (0.09 mmol, 36.6%) of the product as a pale yellow oil.

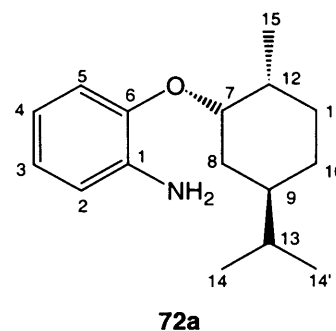


^1H NMR (400 MHz, CDCl_3): δ (ppm) = 4.05 (s, 1H, 14-OH), 4.91 (d, 1H, J = 8.2 Hz, 14-CHOAr), 5.07 (d, 1H, J = 8.2 Hz, 7-CHOH), 6.77 (d, 1H, J = 8.4 Hz, aromatic), 6.82–7.15 (m, 5H, aromatic), 7.18–7.39 (m, 7H, aromatic), 7.83 (d, 1H, J = 8.2 Hz, 2-CH).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 78.9 (14-C), 88.5 (7-C), 116.4, 116.5, 120.9, 121.0, 125.6, 126.0, 127.0, 127.5, 127.6, 128.1, 128.2, 128.3, 128.6, 128.7, 133.9, 134.4, 136.1 (15-C), 137.8 (8-C), 151.6 (6-C).

(–)-1-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-2-aminobenzene (–)-72a

According to GP2 (–)-**71a** (250 mg, 0.90 mmol, 1 eq) was dissolved in methanol (40 mL). After the addition of Pd/C catalyst (8 mg) the mixture was stirred under the atmosphere of hydrogen for 5.5 hours. After filtration and solvent evaporation under reduced pressure, the crude product (207.3 mg, 0.838 mmol, 93%) was used without further purification.



^1H NMR (400 MHz, CDCl_3): δ (ppm) = 0.83 (d, 3H, J = 6.9 Hz,

15-CH₃), 0.91–0.95 (m, 1H, menthyl), 0.93 (d, 3H, *J* = 6.5 Hz, 14-CH₃), 0.95 (d, 3H, *J* = 7.0 Hz, 14'-CH₃), 1.00–1.06 (m, 1H, menthyl), 1.08–1.19 (m, 1H, menthyl), 1.41–1.51 (m, 1H, menthyl), 1.53–1.60 (m, 1H, menthyl), 1.72–1.80 (m, 2H, menthyl), 2.17–2.23 (m, 1H, menthyl), 2.25–2.34 (m, 1H, menthyl), 3.81 (s, 2H, NH₂), 4.09 (dt, 1H, *J* = 10.5, 3.9 Hz, 7-CH), 6.70–6.81 (m, 3H, aromatic), 6.84 (d, 1H, *J* = 7.5 Hz, 5-CH).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 17.1 (15-C), 21.3 (14- or 14'-C), 22.6 (14'- or 14-C), 24.0, 26.5, 31.8, 35.0, 40.9, 48.5, 78.2 (7-C), 113.5, 115.8, 118.8, 121.2, 137.8, 145.9 (6-C).

[α]_D^{24.9} = -90.4 (c = 0.35, CHCl₃).

IR (neat): ν (cm⁻¹) = 3472.8 (w) (H₂O), 3375.7 (w), 2955.1 (w), 1602.8 (s), 1501.3 (s), 1452.8 (m), 1280.2 (m), 1015.9 (m), 740.8 (s).

LRMS: *m/z* (EI) = 248.3 (1), 110.1 (9), 109.0 (100), 108.0 (12), 81 (13), 80.1 (40), 55.1 (32), 43.2 (53).

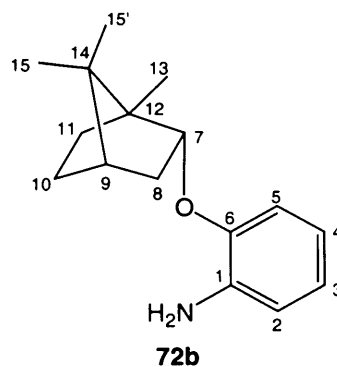
HRMS: *m/z* (ESI) = measured: 248.2011, C₁₆H₂₄ON⁺H⁺ calculated: 248.2009

(-)-(1*R*,2*S*,4*S*)-1,7,7-Trimethyl-2-(2-aminophenyl)oxy-bicyclo[2.2.1]heptane (-)-72b

According to GP2 (-)-**71b** (250 mg, 0.91 mmol, 1 eq) of was dissolved in methanol (40 mL). After the addition of Pd/C catalyst (8 mg) the mixture was stirred under the hydrogen atmosphere for 5.5 h. After filtration the crude product (212.8 mg, 0.87 mmol, 96%) was used without further purification.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 0.92 (s, 3H, 13-CH₃), 0.95 (s, 6H, 15,15'-CH₃), 1.16 (dd, 1H, *J* = 13.4, 3.2 Hz, borneyl), 1.25–1.32 (m, 1H, borneyl), 1.35–1.44 (m, 1H, borneyl), 1.71–1.82 (m, 2H, borneyl), 2.17–2.24 (m, 1H, borneyl), 2.33–2.42 (m, 1H, borneyl), 4.32–4.36 (m, 1H, 7-CH), 6.65–6.69 (m, 2H, aromatic), 6.71–6.76 (m, 2H, aromatic).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 13.9 (13-C), 19.0 (15- or 15'-C), 19.8 (15'- or 15-C), 27.2, 28.0, 37.1, 45.2, 47.63, 49.7, 83.1 (7-C), 112.5, 115.1, 118.5, 120.7, 136.6, 146.6 (6-C).



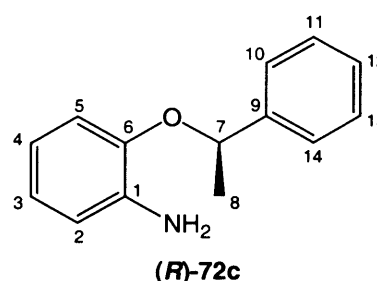
IR (neat): ν (cm^{-1}) = 3465.6 (w) (H_2O), 3379.1 (w), 2983.8 (w), 3872 (w), 1602 (s), 1503.8 (s), 1454.4 (s), 1386.6 (m), 1361.6 (m), 1283 (w), 1275.3 (s), 1219.7 (s), 1145.6 (s), 1108.5 (m), 1015.9 (m), 738.0 (s).

LRMS: m/z (ESI) = 254.2 (4), 137.1 (7), 109.0 (46), 108.0 (25), 95.1 (19), 81.1 (52), 80.1 (100), 69.1 (21), 67.1 (26), 65.0 (20), 53.1 (43), 43.2 (25), 41.2 (78).

HRMS: m/z (ESI) = measured: 246.1852, $\text{C}_{16}\text{H}_{23}\text{ON}^+\text{H}^+$ calculated: 246.1852

(*R*)-1-(2-Phenylamino)-1-phenylethyl ether (*R*)-72c

According to GP2 (*R*)-71c (943 mg, 3.88 mmol, 1 eq) was dissolved in MeOH (50 mL). After addition of Pd/C catalyst (8 mg) the mixture was stirred under hydrogen atmosphere for 4 hours. After filtration and evaporation of the solvent under reduced pressure, the crude product (784.4 mg, 3.68 mmol, 95 %) was used without further purification.



^1H NMR (250 MHz, CDCl_3): δ (ppm) = 1.58 (d, 3H, J = 6.4 Hz, 8- CH_3), 5.22 (q, 1H, J = 6.4 Hz, 7- CH), 6.45–6.66 (m, 4H, aromatic), 7.15–7.32 (m, 5H, aromatic).

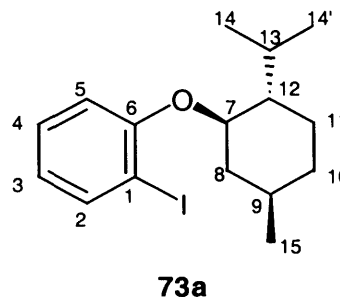
^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 24.7 (8-C), 76.8 (7-C), 114.2, 115.6, 118.7, 121.6, 125.8, 127.8, 128.9, 137.1, 143.6 (9-C), 145.9 (6-C).

$[\alpha]_{\text{D}}^{24.2} = -7.3$ (c = 0.13, CHCl_3).

IR (neat): ν (cm^{-1}) = 1598.8 (s), 1499.9 (s), 1453.3 (s), 1366.1 (m), 1267.2 (s), 1214.8 (s), 1139.2 (m), 1081.0 (s), 1005.3 (m), 929.7 (w), 900.6 (w), 842.4 (w), 737.7 (s), 697.0 (s), 603.9 (w), 545.7 (w).

(-)-1-[[*(1R,2S,5R)*-5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-2-iodobenzene (-)-73a

According to GP3 a suspension of (-)-72a (280 mg, 1.13 mmol, 1 eq) in H₂O and conc. H₂SO₄ (1 mL), a solution of NaNO₂ (93.78 mg, 1.36 mmol, 1.2 eq) was added at 0 °C. This mixture was stirred for 90 hours; ensuring temperature was maintained below 0 °C. Excess acid was then destroyed with urea. Finally, an aqueous solution of KI (225.64 mg, 1.359 mmol, 1.2 eq) was added and stirred at 50 °C for 2 hours. The reaction was then quenched with *sat.* NH₄Cl (10 mL), extracted with CH₂Cl₂ and dried over Na₂SO₄ to yield a brown oil (219 mg, 0.61 mmol, 54%).



¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.76 (d, 3H, J = 7.0 Hz, 15-CH₃), 0.88–0.95 (m, 1H, menthyl), 0.93 (d, 3H, J = 6.6 Hz, 14-CH₃), 0.93 (d, 3H, J = 7.1 Hz, 14'-CH₃), 1.05–1.16 (m, 2H, menthyl), 1.43–1.51 (m, 1H, menthyl), 1.61–1.67 (m, 1H, menthyl), 1.71–1.77 (m, 2H, menthyl), 2.10–2.14 (m, 1H, menthyl), 2.28–2.35 (m, 1H, menthyl), 4.09 (dt, 1H, J = 10.0, 5.0 Hz, 7-CH), 6.58 (dt, 1H, J = 7.5, 1.2 Hz, 5-CH), 6.82 (dd, 1H, J = 8.3, 0.7 Hz, 3-CH), 7.24–7.30 (m, 1H, 4-CH), 7.77 (dd, 1H, J = 6.2, 1.6 Hz, 2-CH).

¹³C NMR (500 MHz, CDCl₃): δ (ppm) = 16.9 (15-C), 21.2 (14'- or 14-C), 22.5 (14- or 14'-C), 23.9, 26.4, 31.8, 34.8, 40.5, 48.2, 79.2 (7-C), 88.3 (1-C), 113.3, 122.3, 129.6, 139.9, 157.2 (6-C).

$[\alpha]_D^{23.8} = -69.0$ (c = 0.58, CHCl₃).

IR (neat): ν (cm⁻¹) = 2950.5 (s), 2869.3 (s), 1581.9 (m), 1465.1 (s), 1378.8 (w), 1277.3 (m), 1236.7 (s), 1180.9 (w), 1155.5 (w), 1114.9 (w), 1099.7 (w), 1038.8 (w), 1013.4 (m), 744.4 (m).

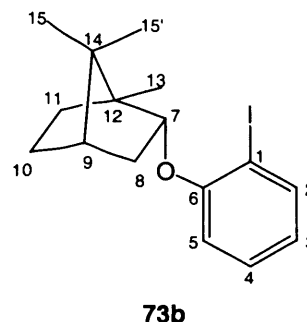
LRMS: m/z (EI) = 358.1 (29), 220.0 (74), 151.1 (9), 138.2 (100), 123.2 (17), 95.2 (42), 83.2 (50), 81.2 (46), 55.1 (34).

HRMS: m/z (EI) = measured: 358.0788, C₁₆H₂₃OI calculated: 358.0788.

(-)-(1R,2S,4S)-1,7,7-Trimethyl-2-(2-iodophenyl)oxy-bicyclo[2.2.1]heptane (-)-73b

According to GP3, (-)-**72b** (280 mg, 1.02 mmol, 1 eq) was stirred with NaNO_3 (84.2 mg, 1.36 mmol, 1.2 eq) and KI (202.6 mg, 1.36 mmol, 1.2 eq). After work-up, product was obtained in good yields of 70% (317.0 mg, 0.71 mmol) as a red-brown oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 0.93 (s, 3H, 13- CH_3), 0.94 (s, 3H, 13'- CH_3), 0.98 (s, 3H, 14- CH_3), 1.13 (dd, 1H, $J = 13.4, 3.2$ Hz, borneyl), 1.28–1.33 (m, 1H, borneyl), 1.36–1.43 (m, 1H, borneyl), 1.73–1.83 (m, 2H, borneyl), 2.34–2.42 (m, 1H, borneyl), 2.44–2.52 (m, 1H, borneyl), 4.32–4.38 (m, 1H, 7- CH), 6.65 (d, 1H, $J = 7.8$ Hz, 5- CH), 7.22–7.28 (m, 1H, aromatic), 7.63 (dd, 1H, $J = 8.2, 1.6$ Hz, 2- CH).



^{13}C NMR (62.5 MHz, CDCl_3): δ (ppm) = 14.2 (13-C), 19.3 (15- or 15'-C), 20.1 (15'- or 15-C), 27.6, 28.2, 36.9, 45.5, 47.8, 50.2, 87.5 (7-C), 113.2, 122.2, 129.6, 139.6, 157.7 (6-C).

$[\alpha]_{\text{D}}^{23.4} = -25.0$ ($c = 0.11$, CHCl_3).

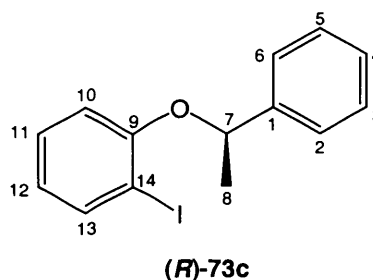
IR (neat): ν (cm^{-1}) = 3059.4 (w) (H_2O), 2946.8 (s), 2876.8 (m), 1575.8 (m), 1464.0 (s), 1388.7 (w), 1368.6 (w), 1278.2 (m), 1248.0 (s), 1137.5 (m), 1111.0 (w), 1048.7 (m), 1023.3 (m), 891.4 (w), 845.7 (w), 744.2 (s).

LRMS: m/z (EI) = 356.1 (21), 220.0 (14), 153.1 (9), 138.2 (12), 137.2 (100), 136.2 (27), 121.2 (7), 81.2 (84), 77.1 (21), 69.1 (18), 43.9 (10), 40.9 (15).

HRMS: m/z (EI) = measured: 356.0630, $\text{C}_{16}\text{H}_{21}\text{OI}$ calculated: 356.0632

(R)-1-(2-Iodophenyl)-1-phenylethyl ether (R)-73c

75 mg (0.31 mmol) of (*R*)-**72c** in H_2O (0.5 mL) and HCL (0.11 mL, conc.) was treated with a solution of NaNO_2 (25.3 mg) in H_2O (0.1 mL) at 0 °C for 40 min. The reaction mixture was slowly transferred into a solution of KI (60.9 mg) in H_2O (0.15 mL) at 0 °C. The reaction mixture was then stirred 5 minutes at rt, 15 min at 45 °C and 15 min at 80 °C. Then the mixture was



cooled to 0 °C and quenched with aqueous saturated $\text{Na}_2\text{S}_2\text{O}_3$ (1 M). The aqueous phase was extracted with ethylacetate, washed with brine and the solvent was evaporated under reduced pressure to yield the product in 54% (61.8 mg, 0.19 mmol) as a deep red oil.

^1H NMR (250 MHz, CDCl_3): δ (ppm) = 1.61 (d, 3H, J = 6.4 Hz, 8- CH_3), 5.28 (q, 1H, J = 6.4 Hz, 7- CH), 6.52–6.73 (m, 1H, aromatic), 6.82–7.13 (m, 2H, aromatic), 7.15–7.41 (m, 5H, aromatic), 7.63–7.71 (m, 1H, 13- CH).

^{13}C NMR (62.5 MHz, CDCl_3): δ (ppm) = 24.5 (8-C), 87.7 (7-C), 114.2, 115.9, 120.9, 122.5, 125.7, 127.6, 129.1, 129.7, 139.5 (1-C).

$[\alpha]_{\text{D}}^{25.0} = -37.2$ (c = 0.04, CHCl_3).

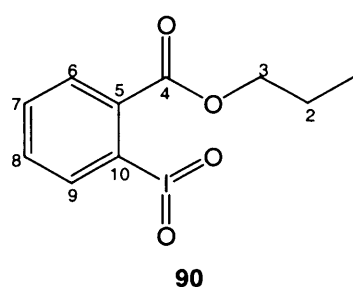
IR (neat): ν (cm^{-1}) = 3061.7 (w) (H_2O), 3010.9 (w), 2980.5 (m), 2919.6 (w), 1581.6 (m), 1470.0 (s), 136.4 (w), 1241.5 (s), 1070.8 (m), 1015.6 (m), 929.9 (w), 825.3 (w), 751.8 (s), 698.9 (m).

LRMS: m/z (EI) = 356.1 (21), 220.0 (14), 153.1 (9), 138.2 (12), 137.2 (100), 136.2 (27), 121.2 (7), 81.2 (84), 77.1 (21), 69.1 (18), 43.9 (10), 40.9 (15).

HRMS: m/z (EI) = measured: 356.0630, $\text{C}_{16}\text{H}_{21}\text{OI}$ calculated: 356.0632

2-Iodoxybenzoic acid propylester **90**

According to GP10 (58.0 mg, 0.20 mmol) of 2-iodobenzoic acid *n*-propylester **89** was stirred together with NaOCl (2.0 mL) and glacial AcOH (0.2 mL) in CH_2Cl_2 (8 mL) at room temperature for 3 d. The brown mixture was extracted with CH_2Cl_2 (5 x 5 mL) and the combined organic phases washed with aqueous, saturated NaHCO_3 and dried over MgSO_4 to yield 60% (38.8 mg,



0.12 mmol) of **90** as a white solid after filtration and solvent evaporation under reduced pressure. Decomposition: >186 °C.

^1H NMR (500 MHz, CDCl_3): δ = 1.02 (t, 3H, J = 7.4 Hz, 1- CH_3), 1.82 (sextet, 2H, J = 7.1 Hz, 2- CH_2), 4.33 (t, 2H, J = 6.7 Hz, 3- CH_2), 7.66 (t, 1H, J = 7.5 Hz, 7- or 8- CH), 7.92 (t, 1H, J = 7.4 Hz, 7- or 8- CH), 8.09 (d, 1H, J = 7.2 Hz, 6- CH), 8.43 (d, 1H, J = 7.9 Hz, 9- CH).

^{13}C NMR (125 MHz, CDCl_3): δ = 10.7 (1-C), 22.1 (2-C), 69.0 (3-C), 125.2, 126.8, 130.6, 132.2, 135.3 (5-C), 149.9 (10-C), 168.4 (4-C).

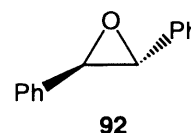
IR (neat): ν (cm^{-1}) = 3417.5 (w) (H_2O), 2965.6 (w), 1679.4 (m), 1584.0 (w), 1463.5 (w), 1393.2 (w), 1302.8 (m), 1142.1 (w), 1112.0 (w), 750.4 (m).

LRMS: m/z (ES) = 322.9 (100), 321.9 (26), 305.9 (12), 280.9 (9), 264.9 (6), 202.1 (3).

HRMS: m/z (ES) = measured: 322.9776, $\text{C}_{10}\text{H}_{12}\text{O}_4\text{I}$ calculated: 322.9780

2,3-Diphenyloxirane **92**

According to GP11 *trans*-stilbene **91** (31.9 mg, 0.177 mmol) was stirred in a solution of DMDO in acetone (1.0 mL) for 8 hours at room temperature. The solvent was evaporated under reduced pressure and the conversion determined from the ^1H NMR spectrum.



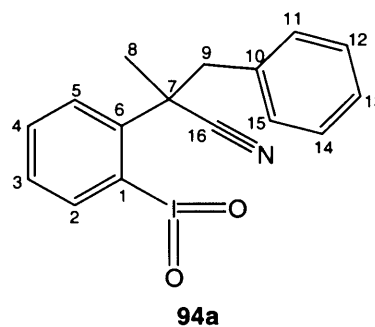
^1H NMR (500 MHz, CDCl_3): δ (ppm) = 3.92 (s, 2H, 2 x PhCHO), 7.28–7.36 (m, 10H, aromatic).

(\pm)-1-Benzyl-1-methyl-1-(2-iodoxyphenyl)acetonitrile **94a**

According to GP11 **40c** (158 mg, 0.46 mmol) was stirred in a solution of DMDO in acetone (0.069 M, 13.2 mL, 0.91 mmol, 2 eq) together with acetic acid (57 μl , 1.0 mmol, 2.2 eq). The solvent was evaporated under reduced pressure to give a white solid.

Yield: 71% (123.8 mg, 0.33 mmol).

^1H NMR (250 MHz, CDCl_3): δ (ppm) = 1.91 (s, 3H, 8- CH_3), 3.23 (d, 1H, J = 13.4 Hz, 9- $\text{CH}_\text{A}\text{H}$), 3.34 (d, 1H, J = 13.4 Hz, 9- $\text{CH}_\text{B}\text{H}$), 7.02 (d, 2H, J = 7.2 Hz, aromatic), 7.24–7.33 (m, 4H, aromatic), 7.49–7.53 (m, 1H, aromatic), 7.62 (t, 1H, J = 7.5 Hz, aromatic), 8.43 (d, 1H, J = 8.0 Hz, 2- CH).



^{13}C NMR (100 MHz, CDCl_3): δ (ppm) = 29.3 (8-C), 39.1 (9-C), 48.6 (7-C), 128.1, 128.5, 129.2, 130.4, 131.2, 131.4, 132.7, 132.8, 134.8, 139.7 (6-C), 148.7, 168.2, 177.1.

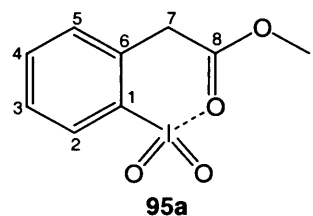
IR (KBr): ν (cm^{-1}) = 2915.4 (w), 1727.6 (s), 1455.8 (m), 1274.3 (s), 1122.6 (m), 1072.8 (m), 769.9 (s), 704.5 (m).

LRMS: m/z (ESI) = 380.1 (5), 365.1 (100), 347.1 (4), 315.2 (3), 297.2 (3), 289.0 (9), 279.1 (2).

HRMS: m/z (ESI) = measured: 380.0146, $\text{C}_{16}\text{H}_{14}\text{O}_2\text{NH}^+$ calculated: 380.0142

(2-Iodoxyphenyl)acetic acid methylester **95a**

According to GP11 **45a** (190.4 mg, 0.69 mmol) was stirred in a solution of DMDO in acetone (0.0657 M, 21.0 mL, 1.38 mmol, 2 eq) for 8 hours at room temperature. A thick white solid emerged immediately after addition of DMDO. The solvent was evaporated to give a white solid (44% yield, 94.2 mg, 0.306 mmol).



Combustion point: 141–142 °C.

^1H NMR (500 MHz, DMSO): δ (ppm) = 3.73 (s, 3H, 9- CH_3), 4.24 (s, 2H, 7- CH_2), 7.40 (d, 1H, J = 7.5 Hz, 5- CH), 7.52 (t, 1H, J = 7.4 Hz, 3- or 4- CH), 7.61 (t, 1H, J = 7.6 Hz, 3- or 4- CH), 7.99 (d, 1H, J = 7.8 Hz, 2- CH).

^{13}C NMR (125 MHz, DMSO): δ (ppm) = 38.6 (7-C), 53.2 (9-C), 127.7, 129.1, 132.3, 132.4, 134.0 (6-C), 151.1 (1-C), 173.6 (8-C).

LRMS: m/z (EI) = 276.0 (5), 231.8 (5), 216.9 (33), 149.0 (100), 121.0 (46), 90.0 (53), 63.0 (32).

HRMS: m/z (EI) = measured: 308.9619, $\text{C}_9\text{H}_9\text{O}_4\text{IH}^+$ calculated: 308.9618

(-)-2-(2-Iodoxyphenyl)acetic acid (3S)-endo-bornylester 95c

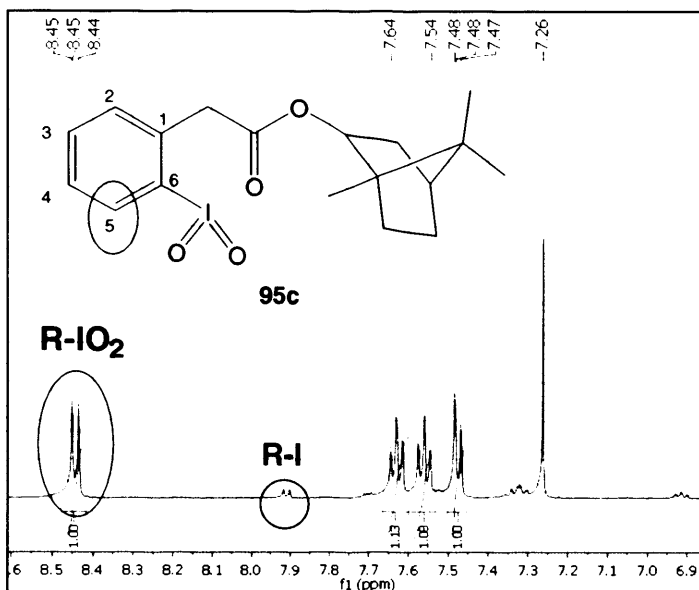
According to GP11 **45c** (61.0 mg, 0.153 mmol) was stirred in a solution of DMDO in acetone (0.0539 M, 3.0 mL, 0.16 mmol, 1.07 eq) for 8 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid. Decomposition: 162 °C.

Conversion: 71%.

No complete NMR was gained because the NMR machine locked

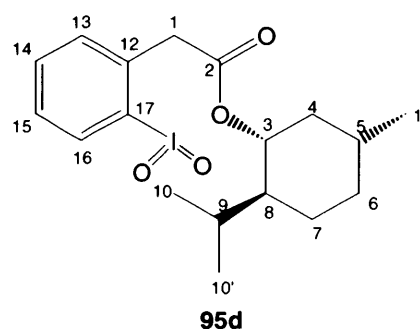
wrongly, so only the aromatic frequencies were obtained. On the other hand, the shift of 5-CH over 8 ppm indicates the formation of the desired product.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.48 (dd, 1H, *J* = 7.9, 1.3 Hz, 2-CH), 7.54–7.58 (m, 1H, 4-CH), 7.61–7.64 (m, 1H, 3-CH), 8.45 (dd, 1H, *J* = 7.9, 1.4 Hz, 5-CH).

**(-)-1-(1-Iodoxyphenyl)acetic acid (3R,5R,8R)-menthylester 95d**

According to GP11 **45d** (59.1 mg, 0.15 mmol) was stirred in a solution of DMDO in acetone (0.0539 M, 3.0 mL, 0.16 mmol, 1.07 eq) for 8 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid.

Conversion: 82%



No suitable NMR was gained due to impurities; therefore conversion determination and characterisation was not possible.

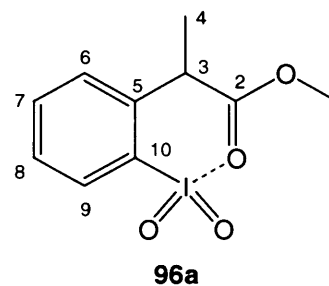
(±)-2-(2-Iodoxyphenyl)propionic acid methylester 96a

According to GP11 **46a** (200.1 mg, 0.69 mmol) was stirred in a solution of DMDO in acetone (0.0657 M, 21.0 mL, 1.38 mmol, 2 eq) for 8 hours at room temperature. The solvent was evaporated to give a white solid (67% yield, 149.7 mg, 0.465 mmol).

m.p. 158 °C.

^1H NMR (500 MHz, DMSO): δ (ppm) = 1.56 (d, 3H, J = 7.0 Hz, 4- CH_3), 3.67 (s, 3H, 1- CH_3), 4.67 (q, 1H, J = 7.0 Hz, 3-CH), 7.46 (dd, 1H, J = 7.2, 1.5 Hz, 6-CH), 7.54–7.60 (m, 2H, 7,8-CH), 8.07 (dd, 1H, J = 7.5, 1.8 Hz, 9-CH).

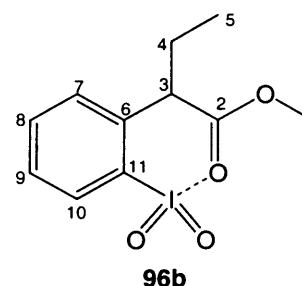
^{13}C NMR (125 MHz, DMSO): δ (ppm) = 18.7 (4-C), 49.7 (3-C), 53.0 (1-C), 128.2, 128.9, 129.5, 132.6, 140.0 (5-C), 151.2 (10-C), 174.4 (2-C).

**(±)-1-Ethyl-1-(2-iodoxyphenyl)acetic acid methylester 96b**

According to GP11 **46b** (208.0 mg, 0.684 mmol) was stirred in a solution of DMDO in acetone (0.054 M, 12.0 mL, 0.648 mmol, 1.06 eq) for 24 hours at room temperature. The solvent was evaporated to give a white solid (63% yield, 143.9 mg, 0.428 mmol). Combustion point: 166 °C.

^1H NMR (500 MHz, DMSO): δ (ppm) = 0.88 (t, 3H, J = 7.3 Hz, 5- CH_3), 1.83–1.92 (m, 1H, 4- CH_AH), 2.09–2.18 (m, 1H, 4- CH_BH), 3.61 (s, 3H, 1- CH_3), 4.25 (dd, 1H, J = 8.4, 6.5 Hz, 3-CH), 7.41 (dd, 1H, J = 6.2, 1.3 Hz, aromatic), 7.48–7.54 (m, 3H, aromatic), 8.03–8.05 (m, 1H, 10-CH).

^{13}C NMR (125 MHz, DMSO): δ (ppm) = 11.8 (5-C), 24.7 (4-C), 49.5 (3-C), 52.0 (1-C), 124.9, 128.1, 128.2, 131.7, 137.2 (6-C), 150.7 (11-C), 172.9 (2-C).

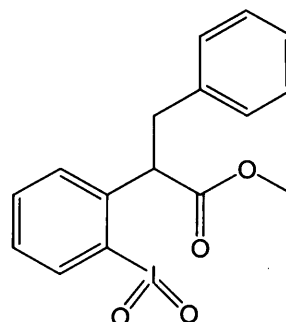


(±)-2-Benzyl-2-(2-iodoxyphenyl)acetic acid methylester 96c

According to GP11 **46c** (58.7 mg, 0.16 mmol) was stirred in a solution of DMDO in acetone (0.0539 M, 3.0 mL, 0.16 mmol, 1 eq) for 8 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid.

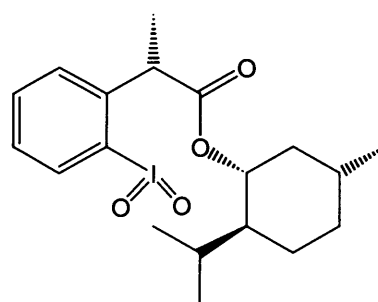
Yield 51% (31.8 mg, 0.08 mmol).

No suitable NMR was gained due to impurities; characterisation was not possible.

**96c****2-(2-Iodoxyphenyl)propionic acid (4*R*,6*R*,9*R*)-menthylester (2*S*)-96f**

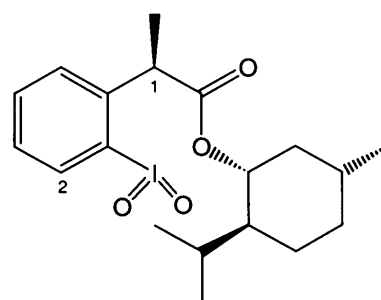
According to GP11 (2*S*)-**46f** (60.5 mg, 0.146 mmol) was stirred in a solution of DMDO in acetone (0.0539 M, 8.0 mL, 0.43 mmol, 3 eq) for 8 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid.

No suitable NMR was gained due to impurities; therefore conversion determination and characterisation was not possible.

**(2*S*)-96f****2-(2-Iodoxyphenyl)propionic acid (4*R*,6*R*,9*R*)-menthylester (2*R*)-96f**

According to GP11 (2*R*)-**46f** (60.5 mg, 0.146 mmol) was stirred in a solution of DMDO in acetone (0.0539 M, 8.0 mL, 0.43 mmol, 3 eq) for 8 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid.

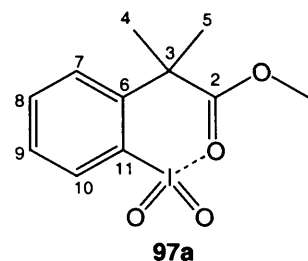
*No suitable NMR was gained due to superimposed frequencies of starting material (2*R*)-46f; however, the distinguishable frequencies of the 1-CH and 2-CH protons were visible, thus marking the formation of (2*R*)-96f and enabling the conversion determination.*

**(2*R*)-96f**

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 4.71–4.77 (m, 1H, 1-CH), 8.09–8.12 (m, 1H, 2-CH)

1,1-Dimethyl-1-(2-iodoxyphenyl)acetic acid methylester 97a

According to GP11 **47a** (622.0 mg, 2.046 mmol) was stirred in a solution of DMDO in acetone (0.069 M, 60.0 mL, 4.092 mmol, 2 eq) together with acetic acid (258 μ l, 4.5 mmol, 2.2 eq) for 24 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid (74% yield, 507.1 mg, 1.509 mmol).



^1H NMR (500 MHz, CDCl_3): δ (ppm) = 1.77 (s, 6H, 4,5- CH_3), 3.82 (s, 3H, 1- CH_3), 7.49–7.55 (m, 3H, 7,8,9- CH), 8.37 (d, 1H, J = 7.5 Hz, 10- CH).

^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 29.1 (4,5-C), 47.2 (3-C), 54.5 (1-C), 127.5, 127.6, 129.7, 133.0, 142.6 (6-C), 150.1 (11-C), 180.5 (2-C).

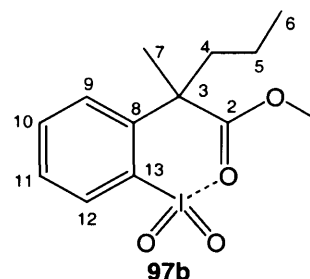
IR (neat): ν (cm^{-1}) = 3417.5 (m) (H_2O), 2965.6 (m), 1699.5 (s), 1458.4 (s), 1433.3 (m), 1282.7 (s), 1252.6 (s), 1152.1 (s), 1101.9 (m), 976.4 (m), 850.9 (m), 775.5 (s), 740.4 (s).

LRMS: m/z (ESI) = 337.0 (6), 322.0 (45), 305.0 (3), 196.1 (100), 177.0 (7), 119.1 (4), 52.1 (41), 44.1 (8).

HRMS: m/z (ESI) = $\text{C}_{11}\text{H}_{13}\text{O}_4\text{I}$ calculated: 336.017, was not measured.

(\pm)-2-(2-Iodoxyphenyl)-2-propylpropionic acid methylester 97b

According to GP11 **47b** (83.9 mg, 0.218 mmol) was stirred in a solution of DMDO in acetone (0.0532 M, 4.1 mL, 0.218 mmol, 1 eq) for 8 hours at room temperature. The solvent was evaporated to give a white solid (54% yield, 48.8 mg, 0.117 mmol). Decomposition: >153 $^\circ\text{C}$.



^1H NMR (500 MHz, CDCl_3): δ (ppm) = 0.91 (t, 3H, 6- CH_3), 1.08–1.13 (m, 1H, 5- $\text{CH}_\text{A}\text{H}$), 1.21–1.28 (m, 1H, 5- $\text{CH}_\text{B}\text{H}$), 1.75 (s, 3H, 7- CH_3), 2.02–2.15 (m, 2H, 4- CH_2), 3.87 (s, 3H, 1- CH_3), 7.49 (dd, 1H, J = 7.9, 1.4 Hz, 9- CH), 7.59 (td, 1H, J = 7.9, 1.4 Hz, 10- or 11- CH), 7.67 (td, 1H, J = 7.2, 1.4 Hz, 10- or 11- CH), 8.45 (dd, 1H, J = 8.0, 1.4 Hz, 12- CH).

^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 14.5 (6-C), 18.5 (5-C), 25.2 (7-C), 45.3 (4-C), 51.3 (1-C), 54.5 (3-C), 127.5, 128.4, 129.9, 133.2, 133.7 (8-C), 141.3 (13-C), 180.8 (2-C).

IR (KBr): ν (cm^{-1}) = 3434.6 (m), 3053.1 (w), 2944.1 (s), 2856.9 (m), 1709.0 (s), 1469.2 (m), 1452.8 (s), 1431.0 (s), 1371.1 (w), 1294.8 (m), 1267.5 (s), 1245.7 (s), 1202.1 (m), 1136.7 (s), 1076.8 (m), 973.2 (m). 929.6 (w), 853.3 (w), 771.6 (s), 722.5 (s), 586.3 (w).

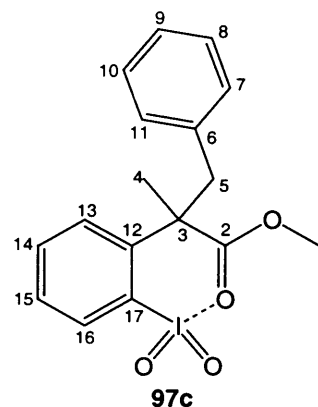
LRMS: m/z (ES) = 729.0 (100), 365.0 (79), 331.0 (1), 232.0 (3), 205.1 (64).

HRMS: m/z (ES) = measured: 365.0235, $\text{C}_{13}\text{H}_{17}\text{O}_4\text{IH}^+$ calculated: 365.0250

(\pm)-1-Benzyl-1-(2-iodoxyphenyl)-1-methylacetic acid methylester **97c**

According to GP11 **47c** (52.3 mg, 0.138 mmol) was stirred in a solution of DMDO in acetone (0.065 M, 4.2 mL, 0.275 mmol, 2 eq) for 24 hours at room temperature. The solvent was evaporated under reduced pressure to give a colourless oil (92% yield, 52.3 mg, 0.127 mmol).

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 1.69 (s, 3H, 4- CH_3), 3.30 (d, 1H, J = 13.6 Hz, (5- CH_A H)), 3.47 (d, 1H, J = 13.7 Hz, 5- $\text{CH}_\text{H}_\text{B}$), 3.82 (s, 3H, 1- CH_3), 6.79 (d, 2H, J = 7.4 Hz, aromatic), 7.13–7.22 (m, 4H, aromatic), 7.38–7.44 (m, 1H, aromatic), 7.51–7.56 (m, 1H, aromatic), 8.44 (d, 1H, J = 8.02 Hz, 16- CH).

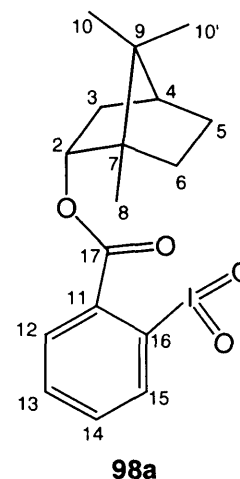


^{13}C NMR (125 MHz, CDCl_3): δ (ppm) = 24.1 (4-C), 48.6 (5-C), 52.0 (3-C), 54.5 (1-C), 127.3, 127.6, 128.6 (3 aromatic C), 129.8, 130.9 (2 aromatic C), 132.6, 135.8, 140.3 (12-C), 150.8 (17-C), 179.8 (2-C).

2-Iodoxyphenyl-1-(1*S*)-endo-bornylether 98a

According to GP11 **60a** (83.9 mg, 0.218 mmol) was stirred in a solution of DMDO in acetone (0.0532 M, 4.1 mL, 0.218 mmol, 1 eq) for 8 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid (54% yield, 48.8 mg, 0.117 mmol). m.p. 150 °C.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.91 (s, 3H, 10-CH₃), 0.93 (s, 3H, 8-CH₃), 0.96 (s, 3H, 10'-CH₃), 1.17 (dd, 1H, *J* = 13.9, 3.5 Hz, bornyl), 1.27–1.34 (m, 1H, bornyl), 1.42–1.48 (m, 1H, bornyl), 1.73–1.86 (m, 2H, bornyl), 2.01–2.13 (m, 1H, bornyl), 2.47–2.53 (m, 1H, bornyl), 5.17–5.22 (m 1H, 2-CH), 7.72 (t, 1H, *J* = 7.5 Hz, 14-CH), 7.95–8.00 (m, 1H, 13-CH), 8.13 (d, 1H, *J* = 7.6 Hz, 12-CH), 8.50 (d, 1H, *J* = 7.8 Hz, 15-CH).



¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 14.0 (8-C), 19.2 (10- or 10'-C), 20.0 (10'- or 10-C), 27.6, 28.3, 37.0, 45.2, 48.4, 49.7, 84.8 (2-C), 123.2, 125.2, 127.3, 130.8, 133.2 (11-C), 135.5 (16-C), 168.8 (17-C).

IR (KBr): ν (cm⁻¹) = 3434.6 (m), 3053.1 (w), 2955.0 (s), 2867.8 (m), 2355.5 (w), 1725.4 (m), 1681.8 (s), 1583.7 (m), 1458.3 (m), 1376.6 (m), 1311.2 (s), 1251.2 (m), 1142.2 (s), 1109.5 (s), 1038.6 (m), 1016.8 (m), 973.2 (m), 886.0 (w), 771.6 (s), 744.3 (s), 678.9 (m), 635.3 (w).

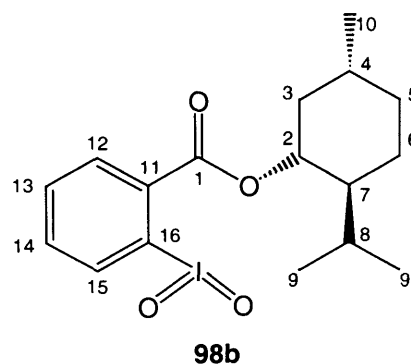
LRMS: *m/z* (ES) = 480.0 (30), 417.0 (9), 384.9 (3), 343.9 (6), 321.9 (100), 304.9 (22), 263.9 (16), 232.0 (5), 213.0 (4).

HRMS: *m/z* (ES) = measured: 417.0554, C₁₇H₂₁O₄IH⁺ calculated: 417.0563

(-)-2-Iodoxybenzoic acid (2*R*,4*R*,7*R*)-menthylester 98b

According to GP11 **60b** (65.4 mg, 0.169 mmol) was stirred in a solution of DMDO in acetone (0.0545 M, 3.1 mL, 0.169 mmol, 1 eq) for 8 hours at room temperature. The solvent was evaporated to give a white solid (64% yield, 45.1 mg, 0.108 mmol). Decomposition: >180 °C.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.79 (d, 3H, *J* = 6.9 Hz, 10-CH₃), 0.82–0.88 (m, 1H, menthyl), 0.93 (d, 3H, *J* =



7.0 Hz, 9-CH₃), 0.95 (d, 3H, J = 6.9 Hz, 9'-CH₃), 1.12–1.18 (m, 1H, menthyl), 1.21 (t, 1H, J = Hz, menthyl), 1.54–1.65 (m, 2H, menthyl), 1.74–1.79 (m, 2H, menthyl), 1.86–1.93 (m, 1H, menthyl), 2.15–2.22 (m, 1H, menthyl), 5.05 (td, 1H, J = 11.1, 4.6 Hz, 2-CH), 7.76 (td, 1H, J = 7.5, 1.0 Hz, 14-C), 8.00 (td, 1H, J = 7.5, 1.3 Hz, 13-C), 8.14 (dd, 1H, J = 7.6, 1.2 Hz, 12-C), 8.53 (d, 1H, J = 7.9 Hz, 15-C).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 16.9 (10-C), 21.0 (9- or 9'-C), 22.2 (9'- or 9-C), 23.9, 26.9, 31.9, 34.3, 40.9, 47.5, 79.5 (2-C), 125.1, 130.8, 133.5, 135.5, 139.5 (11-C), 147.7 (16-C), 167.8 (1-C).

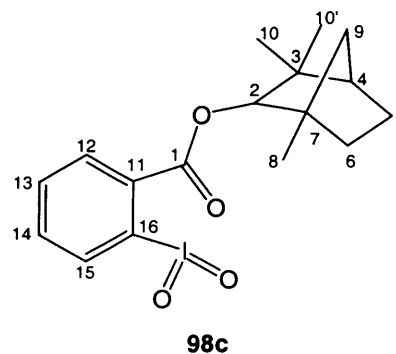
LRMS: m/z (ES) = 482.1 (79), 419.1 (24), 384.9 (12), 343.9 (48), 321.9 (100), 305.9 (54), 288.9 (48), 264.9 (40), 247.9 (38), 232.0 (4), 213.0 (6).

HRMS: m/z (ES) = measured: 419.0711, C₁₇H₂₃O₄IH⁺ calculated: 419.1719

(+)-2-Iodoxybenzoic acid (2*R*)-endo-fenchylester **98c**

According to GP11 **60c** (73.7 mg, 0.192 mmol) was stirred in a solution of DMDO in acetone (0.0539 M, 3.6 mL, 0.192 mmol, 1 eq) for 8 hours at room temperature. The solvent was evaporated under reduced pressure to give a white solid (99% yield, 79.3 mg, 0.19 mmol). m.p. 163 °C.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 0.84 (s, 3H, 8-CH₃), 1.12 (s, 3H, 10-CH₃), 1.20 (s, 3H, 10'-CH₃), 1.20–1.28 (m, 1H, fenchyl), 1.30 (dd, 1H, J = 10.5, 1.4 Hz, fenchyl), 1.51–1.58 (m, 1H, fenchyl), 1.66–1.71 (m, 1H, fenchyl), 1.74–1.82 (m, 2H, fenchyl), 1.85–1.91 (m, 1H, fenchyl), 4.70 (d, 1H, J = 1.1 Hz, 2-CH), 7.74 (td, 1H, J = 7.5, 1.0 Hz, 14-CH), 7.98 (td, 1H, J = 7.8, 1.3 Hz, 13-CH), 8.15 (dd, 1H, J = 7.6, 1.3 Hz, 12-CH), 8.51 (dd, 1H, J = 7.9, 0.8 Hz, 15-CH).



¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 19.8 (8-C), 20.5, 26.0, 27.1, 29.9, 40.4, 41.7, 48.5, 49.1, 90.7 (2-C), 125.2, 127.1, 130.6, 133.3, 135.5 (11-C), 146.3 (16-C), 168.7 (1-C).

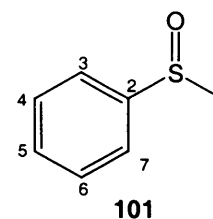
IR (KBr): ν (cm^{-1}) = 3439.5 (m), 3064.0 (w), 2954.9 (s), 2871.5 (m), 2363.5 (w), 2322.6 (w), 1725.4 (m), 1681.8 (s), 1583.7 (m), 1458.3 (m), 1365.7 (m), 1340.0 (s), 1300.3 (s), 1136.8 (s), 1109.5 (s), 1033.2 (m), 984.1 (m), 967.8 (m), 771.6 (s), 738.9 (s), 640.8 (m), 613.5 (m).

LRMS: m/z (ES) = 480.1 (100), 417.1 (19), 384.9 (9), 343.9 (47), 321.9 (46), 305.9 (20), 264.9 (19), 247.9 (13), 165.1 (2).

HRMS: m/z (ES) = measured: 417.0553, $\text{C}_{17}\text{H}_{21}\text{O}_4\text{IH}^+$ calculated: 417.0563

(\pm)-Methylphenylsulfoxide¹ **101**

According to GP26 thioanisole **100** (18.4 mg, 0.148 mmol, 1.5 eq) was stirred in acetonitrile together with (–)-**98a** (41.0 mg, 0.099 mmol, 1 eq) at 80 °C for 4 hours. The crude reaction mixture was poured onto saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with CH_2Cl_2 (5 x 7 mL) and the organic phase dried over Na_2SO_4 ; achieving 99% conversion after filtration, solvent evaporation under reduced pressure and ^1H NMR analysis.

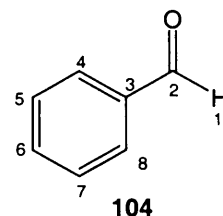


^1H NMR (400 MHz, CDCl_3): δ (ppm) = 2.74 (s, 3H, 1- CH_3), 7.50 (m, 3H, 4,5,6- CH), 7.65–7.67 (m, 3H, 3,7- CH).

HPLC Separation: Chiracel OB-H column, 50:50 hexane:2-propanol, 0.5 mL/min, 20 °C, t_R = 11.0 min (*S*), 16.1 min (*R*).

Benzaldehyde² **104**

According to GP26 benzylalcohol **103** (23.4 mg, 0.191 mmol) was stirred in acetonitrile together with **96b** (64.2 mg, 0.191 mmol, 1 eq) and TFA (15 μL , 0.191 mmol, 1 eq) at 40 °C for 3 hours. The crude reaction mixture was poured onto saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with CH_2Cl_2 (5 x 7 mL) and the organic phase dried over Na_2SO_4 ; achieving 100% conversion after filtration, solvent evaporation and ^1H NMR analysis.



^1H NMR (400 MHz, CDCl_3): δ (ppm) = 7.52–7.55 (m, 2H, 5,7- CH), 7.64 (tt, 1H,

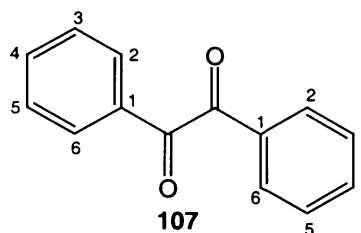
¹ sample was compared to the commercially available compound.

² sample was compared to the commercially available compound.

$J = 6.1, 1.8 \text{ Hz, 6-CH}$), 7.88–7.90 (m, 2H, 4,8-CH), 10.0 (s, 1H, 1-CHO).

Benzil² 107

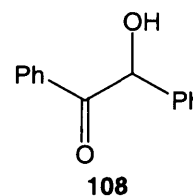
According to GP26 *meso*-hydrobenzoin **106** (64.2 mg, 0.3 mmol) was stirred in CH_2Cl_2 together with **95a** (46.1 mg, 0.15 mmol, 0.5 eq) and TFA (12 μL , 0.15 mmol, 0.5 eq) at room temperature for 3 d. The crude reaction mixture was passed through SiO_2 achieving 100% conversion by ^1H NMR analysis.



^1H NMR (400 MHz, CDCl_3): δ (ppm) = 7.49 (t, 4H, $J = 7.9 \text{ Hz}$, 3,5-CH), 7.6 (t, 2H, $J = 6.3 \text{ Hz}$, 4-CH), 8.13 (d, 4H, $J = 5.3 \text{ Hz}$, 2,6-CH).

(±)-Benzoin³ 108

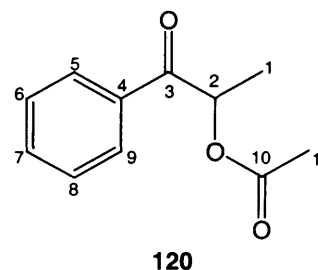
According to GP26 *meso*-hydrobenzoin **106** (19.2 mg, 0.09 mmol) was stirred in acetonitrile together with FIBX **102** (31.6 mg, 0.09 mmol, 1 eq) at room temperature for 4 hours. The crude reaction mixture was poured onto saturated aqueous NaHCO_3 , extracted with CH_2Cl_2 (5 x 7 mL) and the organic phase dried over Na_2SO_4 ; purification by flash column chromatography (petrol ether:diethyl ether 4:1) achieving 64% yield (12.2 mg, 0.06 mmol).



^1H NMR (400 MHz, CDCl_3): δ (ppm) = 4.49 (d, 1H, $J = 5.6 \text{ Hz}$, CHOH), 5.94 (d, 1H, $J = 5.6 \text{ Hz}$, CHOH), 7.19–7.27 (m, 5H, aromatic), 7.33 (t, 2H, $J = 7.9 \text{ Hz}$, aromatic), 7.45 (t, 1H, $J = 7.5 \text{ Hz}$, aromatic), 7.85 (d, 2H, $J = 8.6 \text{ Hz}$, aromatic).

(±)-2-Acetylpropiophenone 120

According to GP8, propiophenone (189.1 mg, 1.41 mmol, 1eq), methyl iodide (20.0 mg, 0.14 mmol, 10 mol%), $\text{BF}_3\text{Et}_2\text{O}$ (599.9 mg, 4.23 mmol, 3 eq) and acetic acid (5.6 mL) were stirred in CH_2Cl_2 . After work-up and flash chromatography, the product was obtained in 51% yield (138.3 mg, 0.72 mmol).



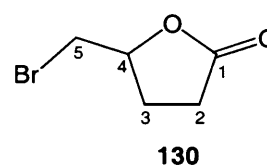
³ sample was compared to the commercially available compound.

^1H NMR (400 MHz, CDCl_3): δ (ppm) = 1.54 (s, 3H, J = 7.1 Hz, 1- CH_3), 2.16 (s, 3H, 11- CH_3), 5.98 (q, 1H, J = 7.1 Hz, 2- CH), 7.39–7.51 (m, 1H, aromatic), 7.57–7.61 (m, 1H, aromatic), 7.92–8.01 (m, 1H, aromatic), 8.07–8.09 (m, 1H, aromatic).

HPLC Separation: Chiracel OD-H column, 90:10 hexane:2-propanol, 0.5 mL/min, 10 °C, t_R = 12.9 min, 20.9 min.

(±)-5-Bromomethyl- γ -butyrolactone 130^[33]

Synthesis according to GP9 from commercially available 4-pentenoic acid **129** (1 eq, 0.9 mmol, 88.6 mg), catalyst **60b** (0.1 eq, 0.09 mmol, 34.2 mg) and freshly recrystallised NBS (1 eq, 0.9 mmol, 157.5 mg).



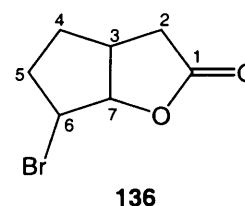
After work-up using saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extraction with CH_2Cl_2 (5 x 5 mL), the organic phase was dried over Na_2SO_4 ; achieving 100% conversion after filtration, solvent evaporation and ^1H NMR analysis.

^1H NMR (250 MHz): δ (ppm) = 2.01–2.18 (m, 1H, 3- CH_AH), 2.34–2.49 (m, 1H, 3- CHH_B), 2.53–2.68 (m, 2H, 2- CH_2), 3.52 (d, 2H, J = 5.1 Hz, 5- CH_2), 4.67–4.77 (m, 1H, 4- CH).

GC (*beta*-column, 150 °C): 14.1 min, 14.4 min.

(±)-6-Bromohexahydrocyclopenta[*b*]furan-2-one 136^[33]

Synthesis according to GP9 from commercially available 2-cyclopentene-1-acetic acid **135** (1 eq, 0.39 mmol, 48.8 mg), catalyst **45e** (0.1 eq, 0.04 mmol, 15.4 mg) and freshly recrystallised NBS (1 eq, 0.39 mmol, 68.9 mg). After work-up using saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extraction with



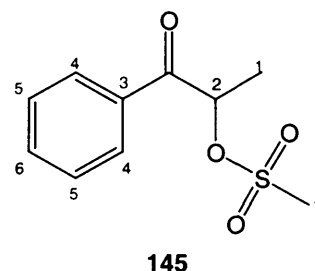
CH_2Cl_2 (5 x 5 mL), the organic phase was dried over Na_2SO_4 ; achieving 98% conversion after filtration, solvent evaporation and ^1H NMR analysis.

^1H NMR (250 MHz): δ (ppm) = 1.55–1.63 (m, 1H, 4- CH_AH), 2.02–2.10 (m, 1H, 4- CHH_B), 2.15–2.25 (m, 1H, 5- CH_AH), 2.30–2.49 (m, 2H, 5- CHH_B , 2- CH_AH), 2.87 (dd, 1H, J = 18.5, 10.2 Hz, 2- CHH_B), 3.10–3.20 (m, 1H, 3- CH), 4.43 (d, 1H, J = 3.6 Hz, 6- CH), 5.06 (d, 1H, J = 6.1 Hz, 7- CH).

HPLC Separation: Chiracel AD column, 70:30 hexane:2-propanol, 0.5 mL/min, 10 °C, t_R = 11.7 min, 14.0 min.

(±)-2-Methanesulfonylpropiophenone^[34] 145

Synthesis according to GP7 from commercially available propiophenone **15** (1 eq, 0.35 mmol, 47.6 mg), catalyst (*S*)-**46f** (10 mol%, 0.035 mmol, 14.7 mg), *m*CPBA (183.6 mg, 1.06 mmol, 3 eq) and 2-methanesulfonic acid **144** (102.3 mg, 1.06 mmol, 3 eq). After work-up using saturated aqueous Na₂S₂O₃, saturated aqueous NaHCO₃ and extraction with CH₂Cl₂ (5 x 8 mL), the organic phase was dried over Na₂SO₄; achieving 39% conversion after filtration, solvent evaporation and ¹H NMR analysis. Yellow oil.

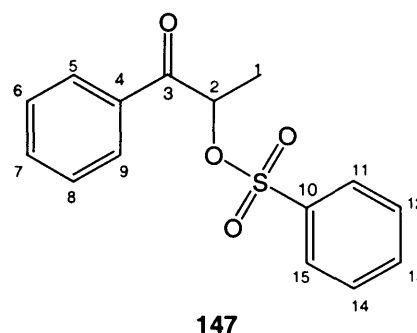


¹H NMR (250 MHz, CDCl₃): δ(ppm) = 1.67 (d, 3H, *J* = 7.0 Hz, 1-CH₃), 3.14 (s, 3H, 7-CH₃), 6.06 (q, 1H, *J* = 7.0 Hz, 2-CH), 7.48–7.54 (m, 2H, 5-CH), 7.60–7.67 (m, 1H, 6-CH), 7.92–7.96 (m, 2H, 4-CH).

HPLC Separation: Chiracel OB-H column, 40:60 hexane:2-propanol, 0.5 mL/min, 40 °C, *t_R* = 22.5 min, 24.9 min.

(±)-2-Benzenesulfonylpropiophenone 147

Synthesis according to GP7 from commercially available propiophenone **15** (1 eq, 49.4 mg, 0.37 mmol), catalyst (+)-**46b** (10 mol%, 0.04 mmol, 11.2 mg), *m*CPBA (190.7 mg, 1.1 mmol, 3 eq) and benzenesulfonic acid **146** (174.8 mg, 1.1 mmol, 3 eq). After work-up using saturated aqueous Na₂S₂O₃, saturated aqueous NaHCO₃ and extraction with CH₂Cl₂ (5 x 8 mL), the organic phase was dried over Na₂SO₄; achieving 98% conversion after filtration, solvent evaporation and ¹H NMR analysis. Yellow oil.



¹H NMR (250 MHz, CDCl₃): δ (ppm) = 1.61 (d, 3H, *J* = 6.9 Hz, 1-CH₃), 5.83 (q, 1H, *J* = 6.9 Hz, 2-CH), 7.43–7.52 (m, 4H, aromatic), 7.56–7.65 (m, 2H, aromatic), 7.86–7.90 (m, 4H, aromatic).

LRMS: m/z (ES) = 290.1 (1), 246.0 (44), 218.0 (28), 185.0 (19), 140.9 (97), 125. (56), 105.0 (99), 77.0 (100).

HRMS: m/z (ES) = measured: 290.0615, $C_{15}H_{14}O_4S$ calculated: 290.0613

HPLC Separation: Chiracel OB-H column, 40:60 hexane:2-propanol, 0.5 mL/min, 40 °C, t_R = 18.8 min, 22.5 min.

(±)-2-Mesitylenesulfonylpropiophenone **149**

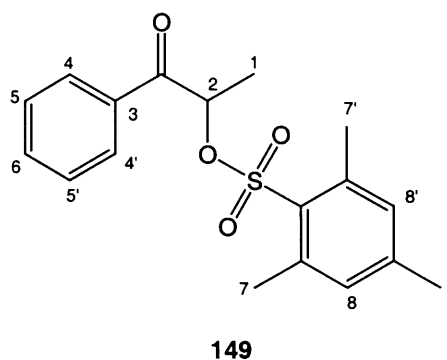
Synthesis according to GP7 from commercially available propiophenone (34.8 mg, 0.26 mmol), catalyst (*R*)-**46g** (10 mol%, 0.03 mmol, 10.7 mg), *m*CPBA (134.4 mg, 0.78 mmol, 3 eq) and 2-mesitylenesulfonic acid (184.1 mg, 0.78 mmol, 3 eq). After work-up using saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and extraction with CH_2Cl_2 (5 x 8 mL), the organic phase was dried over Na_2SO_4 ; achieving 10% conversion after filtration, solvent evaporation and 1H NMR analysis. Yellow oil.

1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.59 (d, 3H, J = 6.9 Hz, 1- CH_3), 2.27 (s, 3H, 9- CH_3), 2.59 (s, 6H, 7,7'- CH_3), 5.74 (q, 1H, J = 6.9 Hz, 2- CH), 6.90 (s, 2H, 8,8'- CH), 7.41–7.48 (m, 2H, 5,5'- CH), 7.58 (tt, 1H, J = 7.4, 1.3 Hz, 6- CH), 7.85–7.90 (m, 2H, 4- CH).

LRMS: m/z (ES) = 332.1 (1), 288.0 (98), 270.0 (49), 240.1 (92), 224.1 (99), 209.1 (16), 183.0 (99), 155.9 (12), 138.9 (22), 105.7 (100), 77.01 (98), 65.0 (19).

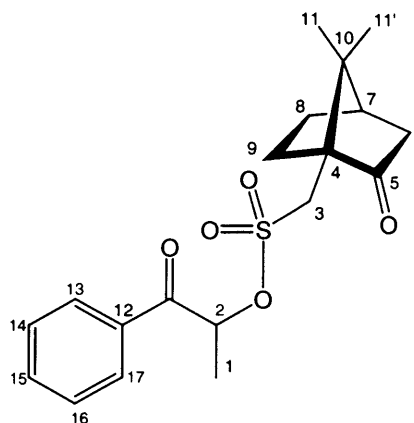
HRMS: m/z (ES) = measured: 332.1090, $C_{18}H_{20}O_4S$ calculated: 332.1082

HPLC Separation: Chiracel AD column, 70:30 hexane:2-propanol, 0.5 mL/min, 10 °C, t_R = 10.9 min, 12.6 min.



(±)-(S/R)-2-Camphorsulfonylpropiophenone^[35] 151/153

Synthesis according to GP7 from commercially available propiophenone **15** (33.2 mg, 0.248 mmol), catalyst (*R*)-**46g** (10 mol%, 0.025 mmol, 10.2 mg), *m*CPBA (128.2 mg, 0.743 mmol, 3 eq) and (1*S*)-(+)-**150** or (1*R*)-(-)-10-camphorsulfonic acid **152** (172.6 mg, 0.743 mmol, 3 eq); purification by preparative TLC (diethylether:petrol ether 1:2). The NMR data of the respective derivative of (*S*)- and (*R*)-camphorsulfonic acid are identical. The diastereomers could not be separated by TLC. Yellow oil.

**151**

Yield: 23% (21.1 mg, 0.6 mmol).

¹H NMR (250 MHz, CDCl₃): δ (ppm) = 0.87 (s, 3H, 11-CH₃), 1.08 (s, 3H, 11'-CH₃) (1.12 ppm for other diastereomer), 1.38–1.47 (m, 1H, Camphor), 1.68 (d, 3H, *J* = 7.0 Hz, 1-CH₃) (1.66 ppm for other diastereomer), 1.97 (d, 2H, *J* = 4.5 Hz, Camphor) (1.90 ppm, *J* = 4.6 Hz for other diastereomer), 2.01–2.13 (m, 2H, Camphor), 2.32–2.35 (m, 2H, Camphor), 3.21 (d, 1H, *J* = 15.0 Hz, 3-CH_A) (3.19 ppm, *J* = 15.1 Hz for other diastereomer), 3.75 (d, 1H, *J* = 15.0 Hz, 3-CH_B) (3.67 ppm, *J* = 15.1 Hz for other diastereomer), 6.06 (q, 1H, *J* = 6.9 Hz 2-CH) (other diastereomer: 6.07 q, 1H, *J* = 6.9 Hz, 2-CH), 7.47–7.54 (m, 2H, 14,16-CH), 7.62 (tt, 1H, *J* = 7.4, 1.3 Hz, 15-CH), 7.94 (t, 1H, *J* = 1.5 Hz, aromatic), 7.96–7.98 (m, 1H, 3-CH, aromatic).

HPLC Separation: Chiracel AD column, 70:30 hexane:2-propanol, 0.5 mL/min, 10 °C, *t_R* = 21.8 min, 28.0 min.

(±)-2-Camphorsulfonyloctaphenone 156

Synthesis according to GP7 from commercially available octanophenone **154** (81.9 mg, 0.401 mmol), catalyst (*S*)-**46f** (10 mol%, 0.04 mmol, 16.6 mg), *m*CPBA (207.5 mg, 1.203 mmol, 3 eq) and (1*S*)-(+)-10-camphorsulfonic acid **150** (279.5 mg, 1.203 mmol, 3 eq); purification by preparative TLC (diethylether:petrol ether 1:2). The diastereomers could not be separated by TLC. Yellow oil. Yield: 23% (40.1 mg, 0.09 mmol).

¹H NMR (250 MHz, CDCl₃): δ (ppm) = 0.83–2.58 (m, 26H, 12-CH, 2,3,4,5,6,11,13, 14-CH₂, 1,16,16'-CH₃), 3.22 (d, 1H, *J* = 15.1 Hz, 8-CH_A), 3.66 (d, 1H, *J* = 15.1 Hz, 8-CH_B), 5.90–5.98 (m, 1H, 7-CH), 7.50–7.64 (m, 3H, 17,18,19-CH), 7.93–7.97 (m, 2H, 16,20-CH).

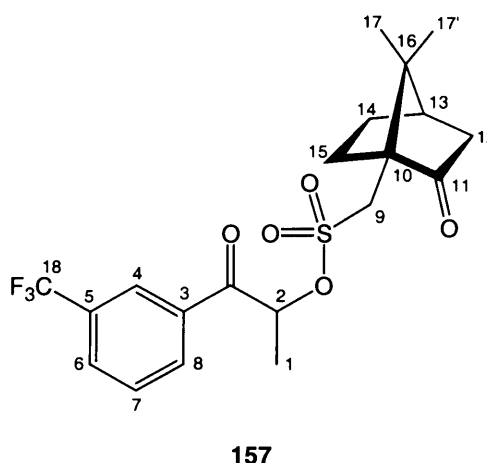
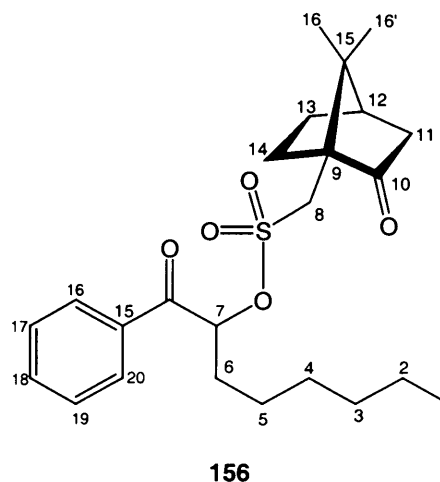
IR (neat): ν (cm⁻¹) = 3426.6 (s) (H₂O), 2960.0 (s), 2926.7 (s), 2860.0 (m), 2360.1 (w), 1741.2 (s), 1696.8 (s), 1596.8 (w), 1446.8 (m), 1357.9 (s), 1252.4 (w), 1224.6 (m), 1174.6 (s), 1052.4 (w), 930.2 (m), 885.8 (w), 819.1 (w), 769.1 (m), 696.9 (m).

HPLC Separation: Chiracel AD column, 70:30 hexane:2-propanol, 0.5 mL/min, 10 °C, *t*_R = 19.7 min, 21.5 min.

(±)-2-Camphorsulfonyl-*m*-trifluoromethylpropiophenone 157

Synthesis according to GP7 from commercially available *m*-trifluoromethylpropiophenone **155** (78.1 mg, 0.386 mmol), catalyst (*S*)-**46f** (10 mol%, 0.04 mmol, 16.0 mg), *m*CPBA (200.0 mg, 1.6 mmol, 3 eq) and (1*S*)-(+)-10-camphorsulfonic acid **150** (269.2 mg, 1.6 mmol, 3 eq); purification by preparative TLC (diethylether:petrol ether 1:2). The diastereomers could not be separated by TLC. Yellow oil.

Yield: 19% (31.8 mg, 0.07 mmol).



^1H NMR (250 MHz, CDCl_3): δ (ppm) = 1.09 (s, 3H, 17- CH_3), 1.12 (s, 3H, 17'- CH_3), 1.47–1.97 (m, 3H, Camphor), 1.68 (d, 3H, J = 6.9 Hz, 1- CH_3), 2.02–2.14 (m, 2H, Camphor), 2.32–2.52 (m, 2H, Camphor), 3.18 (d, 1H, J = 15.2 Hz, 9- CH_A), 3.68 (d, 1H, J = 14.9 Hz, 8- CH_B), 6.01 (q, 1H, J = 6.9 Hz, 2- CH) (6.01 ppm, J = 6.9 Hz for other diastereomer), 7.66 (t, 1H, J = 7.8 Hz, 7- CH), 7.88 (d, 1H, J = 7.4 Hz, 6- CH), 8.15 (d, 1H, J = 7.8 Hz, 8- CH), 8.22 (s, 1H, 4- CH).

IR (neat): ν (cm^{-1}) = 3474.8 (m) (H_2O), 2967.7 (s), 2920.6 (s), 2354.5 (w), 1746.8 (s), 1711.4 (s), 1605.3 (m), 1440.2 (m), 1363.5 (s), 1328.1 (s), 1257.4 (m), 1210.2 (s), 1168.9 (s), 1127.7 (s), 1074.6 (s), 1015.6 (m), 927.2 (s), 809.3 (m), 744.4 (w), 691.3 (w).

LRMS: m/z (ES) = 431.1 (3), 388.1 (1), 332.1 (39), 272.1 (88), 243.1 (35), 212.0 (96), 172.9 (100), 145.0 (95), 106.0 (31).

HRMS: m/z (ES) = measured: 431.1137, $\text{C}_{20}\text{H}_{22}\text{O}_5\text{F}_3\text{S}$ calculated: 431.1140

HPLC Separation: Chiracel AD column, 70:30 hexane:2-propanol, 0.5 mL/min, 10 °C, t_R = 20.4 min, 21.5 min.

5.5 Literature

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Summary and Outlook

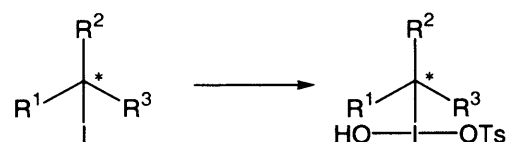
A range of novel enantiomerically pure iodoarenes has been synthesised. Their structures were based on iodoarenes developed by Wirth and co-workers. To access enantiomerically pure compounds, either stereoselective synthesis or racemic resolutions were employed. Two types of reactions were then conducted with these new iodoarenes:

Firstly, they were oxidised to the corresponding hypervalent iodine compounds. After employment of a manifold of strong oxidants, reactions using dimethyldioxirane successfully resulted in the respective λ^5 -iodoarenes. These were employed in enantioselective oxidation reactions of methylphenyl sulphide, benzyl alcohol and *meso*-hydrobenzoin. Oxidations of the sulphide resulted in conversions up to 99%, whereas the enantioselectivity observed was poor (3% ee). The conversions of the oxidation reactions of benzyl alcohol could be enhanced by the employment of trifluoroacetic acid (TFA) from 51% to 100%, probably due to improved dissolving of the iodylarenes by the use of TFA. Oxidation reactions of *meso*-hydrobenzoin resulted in benzaldehyde, when no TFA was added. This phenomenon is probably due to a high oxidation potential of the iodylarenes synthesised. Also, when TFA was present in these reactions, only products resulting from over-oxidation of the *meso*-hydrobenzoin were observed (benzaldehyde and benzil).

Secondly, the enantiomerically pure iodoarenes were employed as catalysts in three different reactions: α -acetoxylation of propiophenone, bromolactonisation of 4-pentenoic acids and α -oxytosylation of propiophenone. Excellent conversions up to 100% were usually observed for the α -acetoxylation, but the enantioselectivity of the reactions did not exceed 8%. For bromolactonisation reactions, two different sources of bromide anions were tested: *N*-bromosuccinimide and tetrabutylammonium bromide. Both methods resulted in excellent conversions up to 100%. Once more, enantioselectivities achieved were poor for both reaction series (up to 6% ee). The α -oxytosylation of propiophenone finally resulted not only in good conversions and yields, but also in very promising enantioselectivities of 39% ee for the employment of *para*-toluenesulfonic acid and 44% ee for the use of (*S*)-camphorsulfonic acid, when a menthyl-derived iodoarene furnished with an additional asymmetric centre in *ortho*-position of the iodine atom was employed as catalyst. Based on this observation, a greater variety of iodoarenes furnished with several chiral centres in *ortho*-position of the iodine atom should be synthesised. In order to further improve selectivities, the reaction mechanism of the α -oxytosylation of propiophenone should be investigated. It could be helpful to compare the keto- and enol-state of the propiophenone by trapping the enol using TBS-Cl. Also, for

probably the first time, alkyl iodides were oxidised *in situ* during this project. In all three catalytic cycles, promising conversions were achieved from the employment of alkyl iodides as catalysts.

This fact opens the possibility of the employment of asymmetric alkyl iodides, where the iodine can be in immediate neighbourhood to the chiral centre. In this way, enhanced enantioselectivities could be achieved, since the “centre-of-action” during a catalytic reaction now would be very close to the asymmetric centre.



Also, the range of iodoarenes furnished with several asymmetric centres should be enlarged and tested, since iodoarenes of this type resulted in best enantioselectivities in all catalytic reactions.

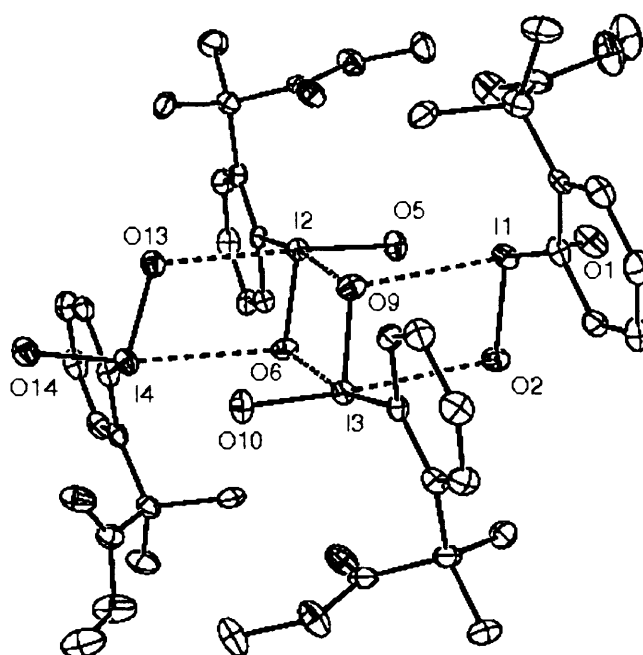
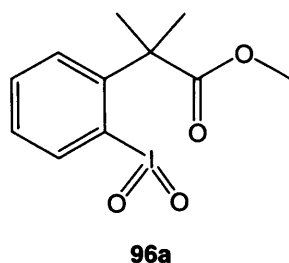


Table 1 Crystal data and structure refinement for **96a**

Identification code	Iodylester	
Empirical formula	C ₄₈ H ₅₈ I ₄ N ₂ O ₁₆	
Formula weight	1426.56	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, Pc	
Unit cell dimensions	$a = 8.2528(17)$ Å	$\alpha = 90^\circ$.
	$b = 13.854(3)$ Å	$\beta = 95.13(3)^\circ$.
	$c = 23.115(5)$ Å	$\gamma = 90^\circ$.
Volume	$2632.3(9)$ Å ³	
Z	2	
Calculated density	1.800 Mg/m ³	
Absorption coefficient	2.436 mm ⁻¹	
F(000)	1400	
Crystal size	0.22 x 0.08 x 0.06 mm	
Theta range for data collection	2.91 to 26.00°.	
Limiting indices	-10 ≤ h ≤ 10, -17 ≤ k ≤ 17, -28 ≤ l ≤ 28	
Reflections collected / unique	9933 / 9923 [R(int) = 0.0326]	

Completeness to theta = 26.00	99.7 %
Absorption correction	Multi scan
Max. and min. transmission	sortav 0.866 and 0.637
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9923 / 2 / 646
Goodness-of-fit on F ²	1.026
Final R indices [I ² sigma(I)]	R1 = 0.0375, wR2 = 0.0728
R indices (all data)	R1 = 0.0445, wR2 = 0.0760
Absolute structure parameter	0.45(2)
Largest diff. peak and hole	0.984 and -0.983 e.Å ⁻³

Table 2 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **96a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
I(1)	10239(1)	6781(1)	2849(1)	29(1)
O(1)	9105(6)	6432(4)	2192(2)	46(1)
N(1)	7452(11)	7260(6)	227(4)	71(2)
C(1)	12530(7)	6123(5)	2679(3)	25(2)
I(2)	8887(1)	8691(1)	3978(1)	23(1)
O(2)	9698(6)	5872(4)	3358(2)	33(1)
N(2)	11971(11)	12387(6)	2994(4)	68(2)
C(2)	13841(9)	6612(5)	2457(3)	24(2)
I(3)	11039(1)	6506(1)	4455(1)	24(1)
O(3)	11274(7)	8474(5)	2215(2)	55(2)
C(3)	15217(8)	6036(6)	2396(3)	34(2)
I(4)	9806(1)	8697(1)	5580(1)	29(1)
O(4)	12245(7)	7775(5)	1455(2)	62(2)
C(4)	15258(9)	5064(6)	2529(3)	38(2)
O(5)	8083(5)	8087(4)	3326(2)	34(1)
C(5)	13912(9)	4604(6)	2724(3)	36(2)
O(6)	8519(6)	7781(3)	4517(2)	29(1)
C(6)	12541(9)	5154(5)	2804(3)	29(2)
O(7)	9679(6)	10141(4)	3183(2)	38(1)
C(7)	13879(9)	7683(6)	2337(3)	35(2)
O(8)	7447(6)	10606(4)	2644(2)	42(1)
C(8)	15307(10)	7988(7)	1995(4)	51(2)
O(9)	11456(6)	7458(3)	3951(2)	32(1)

C(9)	14080(10)	8232(5)	2921(3)	40(2)
O(10)	11837(6)	7017(4)	5131(2)	37(1)
C(10)	12312(10)	8020(6)	1998(3)	38(2)
O(11)	10267(7)	4918(4)	5189(2)	43(1)
C(11)	10702(11)	8067(8)	1129(4)	66(3)
O(12)	12540(6)	4313(4)	5644(2)	45(1)
C(12)	6702(8)	9528(5)	4069(3)	21(1)
O(13)	10083(6)	9482(4)	4971(2)	33(1)
C(13)	6421(8)	10467(5)	3880(3)	25(1)
O(14)	10867(6)	9385(4)	6148(2)	38(1)
C(14)	4855(9)	10824(5)	3943(3)	33(2)
O(15)	9071(6)	7722(4)	6487(2)	47(1)
C(15)	3684(9)	10267(6)	4180(3)	39(2)
O(16)	7701(7)	6463(5)	6764(3)	62(2)
C(16)	4033(8)	9336(5)	4371(3)	32(2)
C(17)	5551(8)	8958(5)	4310(3)	27(2)
C(18)	7700(9)	11124(5)	3635(3)	30(2)
C(19)	9087(9)	11338(5)	4112(3)	37(2)
C(20)	7010(11)	12094(6)	3399(4)	49(2)
C(21)	8389(9)	10578(5)	3135(3)	32(2)
C(22)	8060(10)	10058(6)	2164(3)	45(2)
C(23)	13173(8)	5676(5)	4299(3)	22(1)
C(24)	13402(9)	4690(5)	4419(3)	28(2)
C(25)	14950(9)	4329(5)	4328(3)	33(2)
C(26)	16147(9)	4907(6)	4121(3)	37(2)
C(27)	15879(8)	5864(5)	3998(3)	34(2)
C(28)	14366(8)	6253(5)	4092(3)	27(2)
C(29)	12092(8)	4010(5)	4626(3)	30(2)
C(30)	12727(9)	2982(5)	4763(3)	38(2)
C(31)	10653(9)	3950(6)	4160(3)	34(2)
C(32)	11506(9)	4462(5)	5174(3)	31(2)
C(33)	12073(11)	4766(7)	6178(3)	56(2)
C(34)	7370(8)	9136(5)	5711(3)	28(2)
C(35)	6178(9)	8569(5)	5931(3)	29(2)
C(36)	4701(9)	9073(6)	5995(3)	35(2)
C(37)	4474(9)	10028(6)	5846(3)	39(2)
C(38)	5703(9)	10557(6)	5629(3)	39(2)
C(39)	7158(8)	10104(5)	5557(3)	29(2)
C(40)	6253(8)	7500(5)	6081(3)	31(2)
C(41)	6324(11)	6912(6)	5504(3)	48(2)
C(42)	4765(10)	7130(6)	6372(4)	47(2)
C(43)	7798(9)	7262(5)	6463(3)	34(2)
C(44)	9193(10)	6151(7)	7093(5)	61(3)
C(45)	7301(11)	6627(7)	535(4)	46(2)
C(46)	7138(11)	5838(6)	932(4)	49(2)
C(47)	12276(10)	11721(7)	2755(4)	44(2)
C(48)	12658(10)	10841(6)	2452(3)	46(2)

Table 3 Bond lengths [Å] and angles [°] for **96a**.

I(1)-O(1)	1.779(5)
I(1)-O(2)	1.806(5)
I(1)-C(1)	2.167(6)
N(1)-C(45)	1.143(11)
C(1)-C(6)	1.373(10)
C(1)-C(2)	1.411(9)
I(2)-O(5)	1.797(5)
I(2)-O(6)	1.817(5)
I(2)-C(12)	2.170(6)
N(2)-C(47)	1.116(11)
C(2)-C(3)	1.405(10)
C(2)-C(7)	1.511(10)
I(3)-O(10)	1.787(5)
I(3)-O(9)	1.813(5)
I(3)-C(23)	2.160(6)
O(3)-C(10)	1.207(9)
C(3)-C(4)	1.381(11)
I(4)-O(14)	1.789(5)
I(4)-O(13)	1.809(5)
I(4)-C(34)	2.148(7)
O(4)-C(10)	1.297(9)
O(4)-C(11)	1.477(9)
C(4)-C(5)	1.390(11)
C(5)-C(6)	1.390(10)
O(7)-C(21)	1.221(9)
C(7)-C(10)	1.524(11)
C(7)-C(8)	1.535(10)
C(7)-C(9)	1.546(10)
O(8)-C(21)	1.319(9)
O(8)-C(22)	1.471(9)
O(11)-C(32)	1.205(8)
O(12)-C(32)	1.337(8)
O(12)-C(33)	1.466(9)
C(12)-C(13)	1.385(9)
C(12)-C(17)	1.388(9)
C(13)-C(14)	1.404(9)
C(13)-C(18)	1.540(9)
C(14)-C(15)	1.388(10)
O(15)-C(43)	1.227(8)
C(15)-C(16)	1.385(11)
O(16)-C(43)	1.313(9)
O(16)-C(44)	1.454(10)
C(16)-C(17)	1.377(9)
C(18)-C(21)	1.533(10)
C(18)-C(20)	1.540(10)
C(18)-C(19)	1.546(10)
C(23)-C(28)	1.386(9)

C(23)-C(24)	1.404(9)
C(24)-C(25)	1.405(10)
C(24)-C(29)	1.542(9)
C(25)-C(26)	1.390(10)
C(26)-C(27)	1.370(10)
C(27)-C(28)	1.395(10)
C(29)-C(32)	1.529(10)
C(29)-C(31)	1.532(9)
C(29)-C(30)	1.541(9)
C(34)-C(35)	1.391(10)
C(34)-C(39)	1.395(10)
C(35)-C(36)	1.423(11)
C(35)-C(40)	1.521(10)
C(36)-C(37)	1.376(11)
C(37)-C(38)	1.382(11)
C(38)-C(39)	1.378(10)
C(40)-C(43)	1.521(10)
C(40)-C(42)	1.540(10)
C(40)-C(41)	1.567(10)
C(45)-C(46)	1.442(12)
C(47)-C(48)	1.455(12)

O(1)-I(1)-O(2)	103.0(2)
O(1)-I(1)-C(1)	97.6(2)
O(2)-I(1)-C(1)	95.4(2)
C(6)-C(1)-C(2)	123.7(6)
C(6)-C(1)-I(1)	111.3(5)
C(2)-C(1)-I(1)	125.0(5)
O(5)-I(2)-O(6)	100.4(2)
O(5)-I(2)-C(12)	94.8(2)
O(6)-I(2)-C(12)	96.5(2)
C(3)-C(2)-C(1)	114.6(6)
C(3)-C(2)-C(7)	120.6(6)
C(1)-C(2)-C(7)	124.6(6)
O(10)-I(3)-O(9)	101.4(2)
O(10)-I(3)-C(23)	96.5(2)
O(9)-I(3)-C(23)	94.4(2)
C(4)-C(3)-C(2)	122.4(7)
O(14)-I(4)-O(13)	99.4(2)
O(14)-I(4)-C(34)	98.5(2)
O(13)-I(4)-C(34)	97.1(2)
C(10)-O(4)-C(11)	112.4(7)
C(3)-C(4)-C(5)	120.9(7)
C(6)-C(5)-C(4)	118.4(7)
C(1)-C(6)-C(5)	119.8(7)
C(2)-C(7)-C(10)	111.4(6)
C(2)-C(7)-C(8)	113.2(6)
C(10)-C(7)-C(8)	107.9(6)
C(2)-C(7)-C(9)	108.9(6)
C(10)-C(7)-C(9)	108.6(6)
C(8)-C(7)-C(9)	106.6(6)

C(21)-O(8)-C(22)	114.7(6)
O(3)-C(10)-O(4)	124.7(8)
O(3)-C(10)-C(7)	123.1(7)
O(4)-C(10)-C(7)	112.2(7)
C(32)-O(12)-C(33)	114.9(6)
C(13)-C(12)-C(17)	124.0(6)
C(13)-C(12)-I(2)	126.0(5)
C(17)-C(12)-I(2)	109.8(5)
C(12)-C(13)-C(14)	115.4(6)
C(12)-C(13)-C(18)	124.8(6)
C(14)-C(13)-C(18)	119.8(6)
C(15)-C(14)-C(13)	121.6(7)
C(16)-C(15)-C(14)	120.8(7)
C(43)-O(16)-C(44)	116.1(6)
C(17)-C(16)-C(15)	119.1(7)
C(16)-C(17)-C(12)	119.1(7)
C(21)-C(18)-C(20)	108.3(6)
C(21)-C(18)-C(13)	107.4(6)
C(20)-C(18)-C(13)	113.8(6)
C(21)-C(18)-C(19)	109.4(6)
C(20)-C(18)-C(19)	108.2(6)
C(13)-C(18)-C(19)	109.8(6)
O(7)-C(21)-O(8)	122.4(7)
O(7)-C(21)-C(18)	123.7(7)
O(8)-C(21)-C(18)	113.9(6)
C(28)-C(23)-C(24)	122.9(6)
C(28)-C(23)-I(3)	111.4(5)
C(24)-C(23)-I(3)	125.7(5)
C(23)-C(24)-C(25)	115.2(6)
C(23)-C(24)-C(29)	124.7(6)
C(25)-C(24)-C(29)	120.1(6)
C(26)-C(25)-C(24)	122.0(7)
C(27)-C(26)-C(25)	121.5(7)
C(26)-C(27)-C(28)	118.1(7)
C(23)-C(28)-C(27)	120.3(6)
C(32)-C(29)-C(31)	108.8(6)
C(32)-C(29)-C(24)	106.8(6)
C(31)-C(29)-C(24)	109.6(5)
C(32)-C(29)-C(30)	109.6(6)
C(31)-C(29)-C(30)	108.8(6)
C(24)-C(29)-C(30)	113.2(6)
O(11)-C(32)-O(12)	122.6(7)
O(11)-C(32)-C(29)	124.9(6)
O(12)-C(32)-C(29)	112.6(6)
C(35)-C(34)-C(39)	124.1(6)
C(35)-C(34)-I(4)	126.4(6)
C(39)-C(34)-I(4)	109.5(5)
C(34)-C(35)-C(36)	113.6(7)
C(34)-C(35)-C(40)	128.1(7)
C(36)-C(35)-C(40)	118.2(7)
C(37)-C(36)-C(35)	123.0(7)

C(36)-C(37)-C(38)	120.8(7)
C(39)-C(38)-C(37)	118.6(7)
C(38)-C(39)-C(34)	119.8(7)
C(43)-C(40)-C(35)	111.0(6)
C(43)-C(40)-C(42)	109.5(6)
C(35)-C(40)-C(42)	113.9(6)
C(43)-C(40)-C(41)	106.7(6)
C(35)-C(40)-C(41)	108.5(6)
C(42)-C(40)-C(41)	106.9(6)
O(15)-C(43)-O(16)	120.5(7)
O(15)-C(43)-C(40)	125.7(7)
O(16)-C(43)-C(40)	113.8(6)
N(1)-C(45)-C(46)	178.7(10)
N(2)-C(47)-C(48)	178.8(10)

Table 4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **96a**. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
I(1)	22(1)	40(1)	26(1)	4(1)	5(1)	4(1)
O(1)	27(3)	76(4)	34(3)	4(3)	0(2)	-1(3)
N(1)	78(6)	64(6)	70(6)	14(5)	-1(5)	-20(5)
C(1)	12(3)	42(4)	22(3)	-6(3)	1(2)	8(3)
I(2)	21(1)	25(1)	23(1)	-1(1)	2(1)	1(1)
O(2)	27(3)	36(3)	36(3)	4(2)	11(2)	-4(2)
N(2)	94(7)	55(6)	57(5)	3(4)	11(5)	10(5)
C(2)	22(4)	37(4)	14(3)	0(3)	5(3)	-1(3)
I(3)	21(1)	26(1)	24(1)	-1(1)	2(1)	2(1)
O(3)	41(3)	77(5)	46(3)	9(3)	2(3)	13(3)
C(3)	20(4)	53(5)	28(4)	-3(3)	5(3)	0(3)
I(4)	22(1)	41(1)	24(1)	-1(1)	4(1)	1(1)
O(4)	57(4)	88(5)	40(3)	-14(3)	-9(3)	19(4)
C(4)	33(4)	42(5)	38(4)	-5(3)	5(3)	13(3)
O(5)	27(3)	44(3)	32(3)	-10(2)	1(2)	2(2)
C(5)	37(4)	43(5)	29(4)	-10(3)	-2(3)	4(3)
O(6)	25(2)	25(3)	36(3)	5(2)	5(2)	0(2)
C(6)	30(4)	33(4)	24(4)	2(3)	2(3)	3(3)
O(7)	38(3)	47(3)	30(3)	7(2)	3(2)	11(2)
C(7)	28(4)	46(5)	30(4)	6(3)	-3(3)	-4(3)
O(8)	41(3)	53(3)	31(3)	4(2)	0(2)	-1(3)
C(8)	42(5)	59(6)	53(5)	20(4)	10(4)	-11(4)
O(9)	26(3)	30(3)	39(3)	2(2)	6(2)	0(2)

C(9)	46(5)	29(4)	45(5)	0(3)	2(4)	-9(3)
O(10)	36(3)	41(3)	33(3)	-11(2)	-6(2)	10(2)
C(10)	47(5)	33(4)	38(4)	8(3)	16(4)	0(4)
O(11)	40(3)	58(4)	31(3)	6(3)	11(2)	16(3)
C(11)	50(6)	100(8)	44(5)	-16(5)	-20(4)	12(6)
O(12)	35(3)	72(4)	28(3)	0(3)	0(2)	11(3)
C(12)	19(3)	23(4)	22(3)	-6(3)	3(3)	2(3)
O(13)	29(3)	41(3)	30(3)	-4(2)	7(2)	-6(2)
C(13)	20(3)	29(4)	26(3)	-9(3)	0(3)	3(3)
O(14)	31(3)	53(3)	30(3)	-3(2)	2(2)	-10(2)
C(14)	31(4)	30(4)	37(4)	-4(3)	6(3)	10(3)
O(15)	33(3)	61(4)	45(3)	21(3)	-9(2)	-9(3)
C(15)	22(4)	50(5)	43(4)	-14(4)	1(3)	8(3)
O(16)	32(3)	67(4)	85(5)	36(4)	-14(3)	-9(3)
C(16)	24(4)	38(4)	34(4)	-8(3)	6(3)	-6(3)
C(17)	22(4)	31(4)	26(4)	-2(3)	2(3)	2(3)
C(18)	29(4)	34(4)	28(4)	3(3)	6(3)	-1(3)
C(19)	41(5)	31(4)	40(4)	-12(3)	7(3)	-10(3)
C(20)	61(6)	34(5)	53(5)	1(4)	18(4)	8(4)
C(21)	32(4)	36(4)	27(4)	9(3)	6(3)	-5(3)
C(22)	46(5)	58(6)	31(4)	-8(4)	0(4)	-7(4)
C(23)	18(3)	27(4)	22(3)	-5(3)	2(3)	1(3)
C(24)	29(4)	35(4)	21(3)	1(3)	1(3)	1(3)
C(25)	31(4)	32(4)	39(4)	5(3)	6(3)	11(3)
C(26)	25(4)	46(5)	41(4)	2(4)	7(3)	8(3)
C(27)	21(4)	44(5)	38(4)	-3(3)	5(3)	-9(3)
C(28)	24(4)	26(4)	29(4)	-1(3)	0(3)	-2(3)
C(29)	35(4)	25(4)	31(4)	6(3)	7(3)	2(3)
C(30)	41(4)	26(4)	48(5)	9(3)	6(4)	2(3)
C(31)	30(4)	35(4)	38(4)	-2(3)	1(3)	-5(3)
C(32)	35(4)	26(4)	32(4)	9(3)	2(3)	-2(3)
C(33)	56(6)	85(7)	26(4)	-7(4)	2(4)	0(5)
C(34)	16(3)	41(4)	27(4)	-6(3)	2(3)	1(3)
C(35)	23(4)	41(4)	21(4)	-4(3)	-3(3)	-5(3)
C(36)	23(4)	56(5)	27(4)	-1(3)	-2(3)	-4(3)
C(37)	27(4)	58(5)	32(4)	-9(4)	2(3)	11(4)
C(38)	38(4)	41(5)	38(4)	-10(3)	1(3)	5(4)
C(39)	24(4)	38(4)	25(4)	-4(3)	7(3)	-5(3)
C(40)	28(4)	42(4)	23(4)	3(3)	0(3)	-10(3)
C(41)	69(6)	31(5)	42(5)	11(4)	0(4)	-18(4)
C(42)	36(5)	62(6)	43(5)	17(4)	8(4)	-9(4)
C(43)	34(4)	37(4)	33(4)	4(3)	8(3)	1(3)
C(44)	38(5)	51(6)	92(8)	26(5)	-11(5)	-5(4)
C(45)	43(5)	55(6)	38(5)	-4(4)	-3(4)	-8(4)
C(46)	48(5)	57(6)	44(5)	1(4)	13(4)	-9(4)
C(47)	38(5)	56(6)	37(5)	12(4)	6(4)	-4(4)
C(48)	44(5)	61(6)	34(4)	-7(4)	7(4)	1(4)

Table 5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **96a**.

	x	y	z	U(eq)
H(3)	16153	6326	2259	40
H(4)	16220	4704	2486	45
H(5)	13929	3931	2801	43
H(6)	11614	4860	2945	35
H(8A)	15259	7632	1628	76
H(8B)	16335	7845	2225	76
H(8C)	15239	8682	1915	76
H(9A)	14207	8923	2847	60
H(9B)	15046	7991	3155	60
H(9C)	13116	8128	3131	60
H(11A)	9813	8012	1381	99
H(11B)	10482	7646	791	99
H(11C)	10787	8738	1000	99
H(14)	4590	11464	3819	39
H(15)	2630	10527	4212	46
H(16)	3237	8964	4543	38
H(17)	5808	8317	4430	32
H(19A)	9612	10732	4242	55
H(19B)	8638	11655	4442	55
H(19C)	9890	11763	3956	55
H(20A)	7877	12467	3240	73
H(20B)	6579	12459	3714	73
H(20C)	6135	11974	3092	73
H(22A)	9031	10376	2040	68
H(22B)	7219	10031	1837	68
H(22C)	8338	9401	2295	68
H(25)	15186	3669	4411	40
H(26)	17174	4632	4063	44
H(27)	16700	6252	3852	41
H(28)	14152	6917	4015	32
H(30A)	13677	3014	5049	57
H(30B)	13037	2678	4407	57
H(30C)	11871	2600	4922	57
H(31A)	9756	3599	4315	51
H(31B)	10991	3610	3819	51
H(31C)	10293	4603	4048	51
H(33A)	11849	5453	6106	83
H(33B)	12962	4698	6485	83
H(33C)	11094	4451	6298	83
H(36)	3832	8734	6146	42
H(37)	3459	10328	5894	47
H(38)	5548	11218	5531	47

H(39)	8015	10451	5403	35
H(41A)	7254	7130	5303	72
H(41B)	5317	7014	5254	72
H(41C)	6446	6223	5596	72
H(42A)	4948	6458	6494	70
H(42B)	3796	7167	6096	70
H(42C)	4606	7528	6713	70
H(44A)	10117	6262	6863	92
H(44B)	9118	5461	7182	92
H(44C)	9349	6518	7456	92
H(46A)	7615	5254	780	73
H(46B)	5983	5726	977	73
H(46C)	7704	5998	1311	73
H(48A)	13840	10777	2453	70
H(48B)	12166	10869	2050	70
H(48C)	12223	10284	2649	70

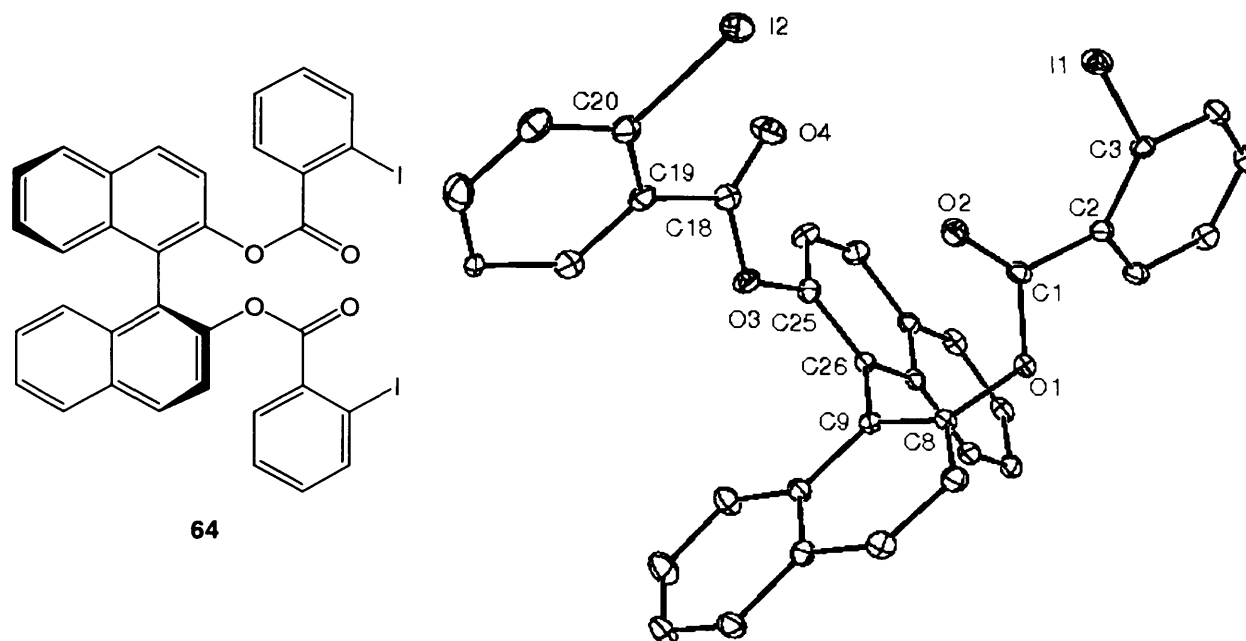


Table 1 Crystal data and structure refinement for **64**.

Identification code	Binaphthyl ester	
Empirical formula	C ₃₄ H ₂₀ I ₂ O ₄	
Formula weight	746.30	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	triclinic, P-1	
Unit cell dimensions	a = 10.724(2) Å	α = 69.55(3)°.
	b = 11.742(2) Å	β = 73.01(3)°.
	c = 13.042(3) Å	γ = 65.32(3)°.
Volume	1377.5(5) Å ³	
Z	2	
Calculated density	1.799 Mg/m ³	
Absorption coefficient	2.322 mm ⁻¹	
F(000)	724	
Crystal size	0.20 x 0.15 x 0.12 mm	
Theta range for data collection	2.93 to 26.99°.	

Limiting indices	-13<=h<=13, -14<=k<=14, -16<=l<=16
Reflections collected / unique	10906 / 5954 [R(int) = 0.0295]
Completeness to theta = 26.99	99.0 %
Max. and min. transmission	sortav 0.767 and 0.599
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5954 / 0 / 361
Goodness-of-fit on F ²	1.031

Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0718
R indices (all data)	R1 = 0.0435, wR2 = 0.0771
Largest diff. peak and hole	0.823 and -0.923 e.Å ⁻³

Table 2 Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for **64**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
I(1)	3231(1)	5017(1)	5044(1)	25(1)
O(1)	-1173(2)	6348(2)	7189(2)	21(1)
C(1)	68(3)	6406(3)	6541(3)	19(1)
I(2)	4869(1)	6226(1)	7538(1)	29(1)
O(2)	1004(3)	6375(3)	6883(2)	29(1)
C(2)	38(3)	6527(3)	5368(3)	19(1)
O(3)	174(2)	8609(2)	8221(2)	24(1)
C(3)	1225(3)	6042(3)	4621(3)	19(1)
O(4)	2111(3)	8543(3)	6928(2)	37(1)
C(4)	1141(4)	6208(3)	3529(3)	23(1)
C(5)	-131(4)	6889(4)	3166(3)	25(1)
C(6)	-1308(4)	7401(4)	3884(3)	25(1)
C(7)	-1233(4)	7215(3)	4981(3)	22(1)
C(8)	-1441(3)	6406(3)	8300(3)	18(1)
C(9)	-1826(3)	7573(3)	8531(3)	17(1)
C(10)	-2313(3)	7617(3)	9670(3)	19(1)
C(11)	-2329(4)	6459(4)	10522(3)	21(1)
C(12)	-1840(4)	5273(3)	10220(3)	23(1)
C(13)	-1427(4)	5246(3)	9132(3)	22(1)
C(14)	-2840(4)	8800(4)	9972(3)	28(1)
C(15)	-3383(4)	8840(4)	11048(3)	35(1)
C(16)	-3399(4)	7693(4)	11885(3)	34(1)
C(17)	-2881(4)	6529(4)	11633(3)	26(1)

C(18)	1556(4)	8377(4)	7883(3)	24(1)
C(19)	2283(4)	7923(3)	8850(3)	22(1)
C(20)	3685(4)	7136(3)	8828(3)	24(1)
C(21)	4351(4)	6857(4)	9696(3)	31(1)
C(22)	3610(5)	7384(4)	10597(3)	36(1)
C(23)	2174(3)	8162(3)	10695(3)	15(1)
C(24)	1550(4)	8387(4)	9793(3)	29(1)
C(25)	-726(3)	9228(3)	7436(3)	20(1)
C(26)	-1777(3)	8766(3)	7629(3)	16(1)
C(27)	-2847(3)	9474(3)	6964(3)	17(1)
C(28)	-2747(4)	10594(3)	6094(3)	20(1)
C(29)	-1599(4)	10976(4)	5906(3)	25(1)
C(30)	-613(4)	10318(4)	6574(3)	27(1)
C(31)	-4022(4)	9118(3)	7148(3)	21(1)
C(32)	-5046(4)	9838(4)	6511(3)	24(1)
C(33)	-4937(4)	10946(4)	5650(3)	24(1)
C(34)	-3825(4)	11311(3)	5446(3)	24(1)

Table 3 Bond lengths [Å] and angles [°] for **64**.

I(1)-C(3)	2.109(3)
O(1)-C(1)	1.367(4)
O(1)-C(8)	1.413(4)
C(1)-O(2)	1.195(4)
C(1)-C(2)	1.495(5)
I(2)-C(20)	2.113(4)
C(2)-C(3)	1.398(5)
C(2)-C(7)	1.401(5)
O(3)-C(18)	1.353(4)
O(3)-C(25)	1.406(4)
C(3)-C(4)	1.393(5)
O(4)-C(18)	1.199(4)
C(4)-C(5)	1.388(5)
C(5)-C(6)	1.378(5)
C(6)-C(7)	1.391(5)
C(8)-C(9)	1.371(5)
C(8)-C(13)	1.411(5)
C(9)-C(10)	1.436(5)
C(9)-C(26)	1.491(5)
C(10)-C(14)	1.414(5)
C(10)-C(11)	1.427(5)
C(11)-C(17)	1.414(5)
C(11)-C(12)	1.421(5)
C(12)-C(13)	1.366(5)
C(14)-C(15)	1.363(5)
C(15)-C(16)	1.409(6)
C(16)-C(17)	1.363(6)
C(18)-C(19)	1.496(5)

C(19)-C(20)	1.397(5)
C(19)-C(24)	1.405(5)
C(20)-C(21)	1.384(5)
C(21)-C(22)	1.395(6)
C(22)-C(23)	1.419(5)
C(23)-C(24)	1.412(5)
C(25)-C(26)	1.371(5)
C(25)-C(30)	1.400(5)
C(26)-C(27)	1.429(5)
C(27)-C(31)	1.419(5)
C(27)-C(28)	1.426(5)
C(28)-C(29)	1.409(5)
C(28)-C(34)	1.422(5)
C(29)-C(30)	1.365(5)
C(31)-C(32)	1.370(5)
C(32)-C(33)	1.413(5)
C(33)-C(34)	1.356(5)

C(1)-O(1)-C(8)	118.5(3)
O(2)-C(1)-O(1)	124.0(3)
O(2)-C(1)-C(2)	126.8(3)
O(1)-C(1)-C(2)	109.2(3)
C(3)-C(2)-C(7)	118.1(3)
C(3)-C(2)-C(1)	123.3(3)
C(7)-C(2)-C(1)	118.4(3)
C(18)-O(3)-C(25)	120.0(3)
C(4)-C(3)-C(2)	120.9(3)
C(4)-C(3)-I(1)	115.5(2)
C(2)-C(3)-I(1)	123.5(3)
C(5)-C(4)-C(3)	119.8(3)
C(6)-C(5)-C(4)	120.1(3)
C(5)-C(6)-C(7)	120.2(3)
C(6)-C(7)-C(2)	120.8(3)
C(9)-C(8)-C(13)	123.1(3)
C(9)-C(8)-O(1)	120.1(3)
C(13)-C(8)-O(1)	116.5(3)
C(8)-C(9)-C(10)	117.8(3)
C(8)-C(9)-C(26)	121.4(3)
C(10)-C(9)-C(26)	120.8(3)
C(14)-C(10)-C(11)	118.5(3)
C(14)-C(10)-C(9)	121.5(3)
C(11)-C(10)-C(9)	119.9(3)
C(17)-C(11)-C(12)	121.8(3)
C(17)-C(11)-C(10)	119.3(3)
C(12)-C(11)-C(10)	118.8(3)
C(13)-C(12)-C(11)	120.9(3)
C(12)-C(13)-C(8)	119.3(3)
C(15)-C(14)-C(10)	120.8(4)
C(14)-C(15)-C(16)	120.7(4)
C(16)-C(17)-C(11)	120.3(4)
O(4)-C(18)-O(3)	123.8(3)

O(4)-C(18)-C(19)	124.8(3)
O(3)-C(18)-C(19)	111.3(3)
C(20)-C(19)-C(24)	118.3(3)
C(20)-C(19)-C(18)	123.1(3)
C(24)-C(19)-C(18)	118.5(3)
C(21)-C(20)-C(19)	120.9(3)
C(21)-C(20)-I(2)	116.4(3)
C(19)-C(20)-I(2)	122.6(3)
C(20)-C(21)-C(22)	119.3(4)
C(21)-C(22)-C(23)	123.2(4)
C(24)-C(23)-C(22)	114.7(3)
C(19)-C(24)-C(23)	123.6(3)
C(26)-C(25)-C(30)	122.8(3)
C(26)-C(25)-O(3)	115.7(3)
C(30)-C(25)-O(3)	121.3(3)
C(25)-C(26)-C(27)	118.4(3)
C(25)-C(26)-C(9)	120.9(3)
C(27)-C(26)-C(9)	120.6(3)
C(31)-C(27)-C(28)	118.6(3)
C(31)-C(27)-C(26)	122.5(3)
C(28)-C(27)-C(26)	118.9(3)
C(29)-C(28)-C(34)	121.5(3)
C(29)-C(28)-C(27)	119.6(3)
C(34)-C(28)-C(27)	118.9(3)
C(30)-C(29)-C(28)	120.7(3)
C(29)-C(30)-C(25)	119.4(3)
C(32)-C(31)-C(27)	120.9(3)
C(31)-C(32)-C(33)	120.1(3)
C(34)-C(33)-C(32)	120.6(3)
C(33)-C(34)-C(28)	120.9(3)

Table 4 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **64**. The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
I(1)	16(1)	30(1)	26(1)	-10(1)	-2(1)	-4(1)
O(1)	23(1)	26(1)	17(1)	-9(1)	1(1)	-12(1)
C(1)	18(2)	16(2)	19(2)	-7(1)	1(1)	-5(1)
I(2)	23(1)	27(1)	32(1)	-9(1)	-3(1)	-5(1)
O(2)	20(1)	42(2)	27(1)	-16(1)	-5(1)	-7(1)
C(2)	17(2)	18(2)	19(2)	-5(1)	0(1)	-7(1)
O(3)	21(1)	30(2)	23(1)	-3(1)	-6(1)	-13(1)
C(3)	14(2)	19(2)	23(2)	-7(1)	-2(1)	-5(1)
O(4)	23(1)	54(2)	22(1)	-8(1)	-2(1)	-6(1)

C(4)	24(2)	23(2)	20(2)	-9(2)	1(2)	-7(2)
C(5)	27(2)	27(2)	21(2)	-8(2)	-5(2)	-9(2)
C(6)	25(2)	25(2)	24(2)	-3(2)	-7(2)	-9(2)
C(7)	17(2)	25(2)	22(2)	-9(2)	0(1)	-6(2)
C(8)	17(2)	23(2)	15(2)	-8(1)	1(1)	-8(1)
C(9)	14(2)	20(2)	18(2)	-6(1)	-2(1)	-6(1)
C(10)	17(2)	24(2)	17(2)	-7(1)	-3(1)	-6(1)
C(11)	19(2)	26(2)	20(2)	-5(2)	-5(1)	-9(2)
C(12)	26(2)	19(2)	21(2)	-1(2)	-6(2)	-8(2)
C(13)	25(2)	19(2)	23(2)	-6(2)	-1(2)	-10(2)
C(14)	35(2)	24(2)	22(2)	-10(2)	-1(2)	-9(2)
C(15)	45(2)	29(2)	30(2)	-16(2)	-1(2)	-9(2)
C(16)	39(2)	49(3)	17(2)	-15(2)	1(2)	-18(2)
C(17)	26(2)	35(2)	16(2)	-4(2)	-3(2)	-13(2)
C(18)	24(2)	24(2)	26(2)	-7(2)	-4(2)	-9(2)
C(19)	23(2)	22(2)	23(2)	-1(2)	-6(2)	-12(2)
C(20)	23(2)	20(2)	28(2)	-8(2)	-3(2)	-9(2)
C(21)	27(2)	29(2)	36(2)	-1(2)	-14(2)	-11(2)
C(22)	50(3)	41(3)	24(2)	0(2)	-16(2)	-22(2)
C(23)	23(2)	14(2)	11(2)	1(1)	-5(1)	-12(1)
C(24)	27(2)	34(2)	28(2)	-8(2)	-4(2)	-13(2)
C(25)	19(2)	21(2)	20(2)	-4(1)	-6(1)	-6(2)
C(26)	21(2)	14(2)	14(2)	-4(1)	-1(1)	-8(1)
C(27)	18(2)	17(2)	17(2)	-9(1)	-1(1)	-4(1)
C(28)	22(2)	18(2)	19(2)	-7(1)	-1(1)	-6(1)
C(29)	28(2)	21(2)	27(2)	-2(2)	-4(2)	-12(2)
C(30)	24(2)	26(2)	32(2)	-4(2)	-5(2)	-14(2)
C(31)	22(2)	22(2)	21(2)	-8(2)	0(1)	-8(2)
C(32)	19(2)	29(2)	26(2)	-15(2)	-1(2)	-7(2)
C(33)	21(2)	30(2)	18(2)	-10(2)	-5(1)	-1(2)
C(34)	29(2)	19(2)	19(2)	-5(2)	-5(2)	-4(2)

Table 5 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for
64.

	x	y	z	U(eq)
H(4)	1952	5857	3034	28
H(5)	-191	7002	2422	29
H(6)	-2173	7883	3628	30
H(7)	-2053	7557	5473	27
H(12)	-1800	4489	10784	28
H(13)	-1133	4455	8936	27
H(14)	-2815	9576	9417	33
H(15)	-3752	9645	11236	42
H(16)	-3774	7731	12633	41
H(17)	-2892	5763	12206	31
H(21)	5303	6313	9678	37
H(22)	4089	7214	11172	43
H(23)	1672	8504	11317	17
H(24)	583	8879	9827	35
H(29)	-1510	11700	5306	30
H(30)	144	10597	6456	32
H(31)	-4100	8370	7721	25
H(32)	-5830	9591	6648	29
H(33)	-5649	11440	5210	29
H(34)	-3765	12056	4861	28

List of Publications emerged from this Project

- S. M. Altermann, R. D. Richardson, T. K. Page, R. K. Schmidt, E. Holland, U. Mohammed, S. M. Paradine, A. N. French, C. Richter, A. M. Bahar, B. Witulski, T. Wirth **Catalytic Enantioselective α -Oxysulfonylation of Ketones Mediated by Iodoarenes** *Eur. J. Org. Chem.* **2008**, (31), 5315–5328.
- R. D. Richardson, J. M. Zayed, S. Altermann, D. Smith, T. Wirth **Tetrafluoro-IBA and –IBX: hypervalent iodine reagents** *Angew. Chem. Int. Ed.* **2007**, 46(34), 6529–6532.
- R. D. Richardson, T. K. Page, S. M. Altermann, S. M. Paradine, A. N. French, T. Wirth **Enantioselective α -oxytosylation of ketones catalyzed by iodoarenes** *Synlett* **2007** (4), 538–542.

